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Chemical Oscillations

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Under constant external conditions, chemical reactions may also proceed in a rhythmic manner. The kinetic mechanisms responsible for such oscillations prove to be unexpectedly complicated. It can nevertheless be demonstrated that chemical periodicity is caused by certain kinds of coupling between simultaneous reactions or transport processes. A general survey of the chemistry and phenomenology of the principal chemical oscillations is followed by a discussion of the situations leading to periodic reactions on the basis of the multivariable kinetics of feedback systems. Autocatalysis and autoinhibition play an important role, as also do kinetic instability and spatial propagation.

1. Introduction

Left to themselves under constant external conditions, normal chemical reaction systems equilibrate provided they are not completely inhibited. Thermodynamically open systems approach a likewise thermodynamically defined steady state, as shown schematically in a plot of concentration *versus* time (Fig. 1a).

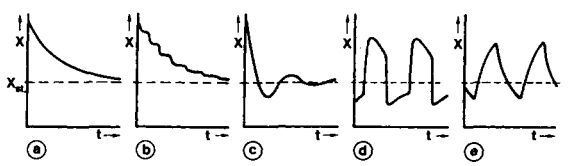


Fig. 1. Temporal behavior of thermodynamically open systems. X = concentration of starting compound. a) Normal non-periodic attainment of steady state; b) attainment of steady state at rhythmically changing rate; c) attainment of steady state *via* attenuated oscillation; d) flip-flop oscillation; e) sawtooth oscillation.

However, in their experimental work chemists, chemical engineers, and biologists are also acquainted with numerous examples of chemical systems deviating considerably from this pattern in their temporal behavior (cf. also Fig. 1b and 1c). One of the most interesting deviations is the ability of some chemical and physicochemical systems to undergo spontaneous oscillatory reaction (Fig. 1d and 1e).

Although this phenomenon of rhythmic chemical, and especially electrochemical, reactions has long been known, thorough experimental and theoretical studies have only been performed in the past 20 years. Several competent reviews of this field have recently been published (see *e.g.* [1–4]). In the present article, recent discoveries and viewpoints will be

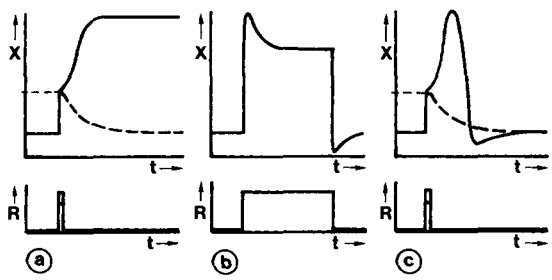


Fig. 2. Non-periodic behavior patterns of systems with kinetic coupling. a) Excitable bistability; b) overshoot behavior; c) excitable pulse formation. R is an external stimulus acting transiently on the system (see also Fig. 21). The broken lines indicate subthreshold behavior.

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evaluated to show that, in spite of the unexpected complexity of their mechanisms, the kinetics of oscillatory chemical reactions can probably be reduced to a limited number of kinetic principles, and is largely analogous to the kinetics of known mechanical and electrical systems.

Closely connected with chemical periodicity are other "anomalous" non-periodic modes of behavior, some of which are illustrated in Figure 2. They generally occur on slight modification of systems capable of oscillation. Systems no longer able to oscillate generally still possess bistability, *i.e.* they can exist in two stable reaction states whose interconversion can be triggered by external perturbations ("stimuli"). The study of non-periodic behavior is of great value for the assessment of oscillatory kinetics. It also underlines the close relationship with the excitation processes of nerve and muscle cells, which are themselves known to be capable of oscillatory behavior.

The phenomena mentioned have their origin in kinetic processes which are not observed in "normal" systems. A detailed account presented in Section 3.3 shows that mainly kinetic coupling exists between the effective reactions of the oscillatory system and gives rise to various forms of chemical feedback. As in mechanical and electrical systems, the generation of oscillations in chemical systems is also a consequence of feedback processes. Studies should therefore concentrate on the question how chemical feedback can come about, and what form it must take for oscillations to occur.

Chemical oscillations in homogeneous systems are currently under investigation in numerous laboratories. And yet, despite the overwhelming body of detailed factual material and great effort expended, not a single chemical oscillation has so far be completely elucidated beyond all doubt. The reasons are listed below:

Periodic chemical reactions occur only in extensively coupled multivariable systems. Such systems are extremely non-linear with respect to driving forces and the driven fluxes and reactions.

Oscillations affect changes of states far removed from equilibrium, to which the classical theories of the thermodynamics of equilibrium states and non-equilibrium states close to equilibrium are no longer directly applicable.

Oscillatory chemical systems contain unstable states which cause spontaneous rhythmically occurring spatial propagation of changes of state. Hence homogeneous systems in a thermodynamic sense are no longer present.

Section 3 is devoted to these kinetic features and difficulties. Before proceeding further, however, the principal chemical and physicochemical oscillations and their specific phenomenology will first be considered.

2. Phenomenology of Chemical and Physicochemical Oscillations

The external appearance of the oscillations observed in a large variety of systems is surprisingly uniform. The oscillograms either consist of periodic transitions of various degrees of sharpness between two quasi-steady states, or they have a sawtooth shape (Figs. 1d and 1e). Chemical oscillations therefore resemble non-linear flip-flop oscillations more closely than harmonic vibrations. The sinusoidal oscillograms occasionally recorded are by no means due to particularly simple linear processes.

In an open system with a regular flux of reactants the oscillations can be maintained indefinitely. In closed systems, where they were generally first observed, they are of limited duration sufficiently distant from equilibration.

2.1. Chemical Oscillations in Homogeneous Systems

2.1.1. Purely Chemical Oscillations in Homogeneous Solutions

This class of chemical oscillatory reactions presently attracts the greatest interest among both experimentalists and theorists. Oscillations were previously thought to be impossible in homogeneous solutions. The unfounded assumption that periodic behavior always requires the presence of a heterogeneous structure was apparently based on the view that control of the periodic change in the reaction can only be the result of the action of fluctuating interfacial states as known from heterogeneous catalysis.

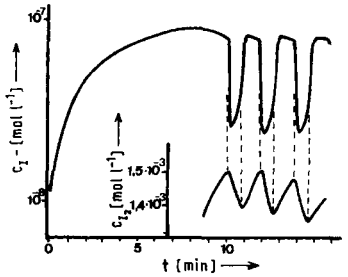


Fig. 3. Bray oscillation: decomposition of hydrogen peroxide in the presence of iodate and iodine. Upper curve, iodide concentration; lower curve, iodine concentration (according to [11]).

When *Bray* observed[5, 6] in 1920 that the decomposition of hydrogen peroxide in the presence of iodic acid and iodine follows a periodic course (Fig. 3), much effort was devoted to the search for the interfacial structures responsible for the oscillations—they were suspected to lie in microscopic oxygen bubbles[7, 8] and also in dust particles[9]. Meanwhile, after the discovery of further "homogeneous" periodically reacting chemical systems, it is known that structural heterogeneity is not necessary for the occurrence of oscillations.

The Bray reaction proceeds according to the simple equation

$$2H_2O_2 \xrightarrow{HIO_3/I_2} 2H_2O + O_2$$

Thus iodic acid and iodine are true catalysts. The usual formulation as two partial equations

$$\begin{array}{lrcl} 1) & 2HIO_3 + 5H_2O_2 & \rightarrow & I_2 + 5O_2 + 6H_2O \\ 2) & I_2 + 5H_2O_2 & \rightarrow & 2HIO_3 + 4H_2O \\ \hline & 10H_2O_2 & \rightarrow & 10H_2O + 5O_2 \end{array}$$

with H_2O_2 reducing the iodic acid and oxidizing the iodine describes the actual reactions occurring only incompletely or even incorrectly. Experimental results show that oxygen evolution is not stoichiometric with the optically observable conversion of iodine, and that the oxygen appears as product of the iodine reaction (2) and not of the iodic acid reaction (1) during the oscillation[2].

Degn[10] interprets these experimental observations in terms of an intermediate higher order branching reaction of a transient radical species. This would explain the non-stoichiometric relationship between the liberation of iodine and O_2 and also the suspected autocatalytic nature of a partial reaction.

Another mechanism has been proposed by *Matsuzaki, Nakajima*, and *Liebhafsky*[11], which comprises four essential reaction steps:

1)	$HIO_3 + H_2O_2$	$\rightarrow HIO_2 + H_2O + O_2$
2)	$HIO_2 + H_2O_2$	$\rightarrow HIO + H_2O + O_2$
3)	$2HIO_2 + HIO + H_2O_2$	$\rightarrow 3HIO_2 + H_2O$
4)	$HIO_2 + H_2O_2$	$\rightarrow HIO_3 + H_2O$
	$4H_2O_2$	$\rightarrow 4H_2O + 2O_2$

The third step is autocatalytic.

This reaction sequence corresponds to a mathematical model of systems capable of oscillation which has been put forward by *Prigogine, Nicolis*, and *Lefever*[12,13]—it has been designated as "Brusselator". The model (cf. Section 3.2) consists of the following four sub-steps:

1)	A	$\rightarrow$ X
2)	B + X	$\rightarrow$ D + X′
3)	2X + X′	$\rightarrow$ 3X
4)	X	$\rightarrow$ E
	A + B	$\rightarrow$ D + E

In the case of the Bray reaction, A and E would correspond to HIO_3, X to HIO_2, X′ to HIO, B to H_2O_2, and D to O_2, the overall balance being:

$$B \rightarrow D$$

because A = E.

The autocatalytic step (3) of the Brusselator and of the reaction model of the Bray reaction is trimolecular. This is the most problematic step of these models because trimolecular reactions are extremely improbable, especially in a reaction mixture like that of the Bray reaction for which 16 possible reactions of 11 reactants have to be considered[11] and in which two bimolecular reactions (2 and 4) are in competition.

In 1951, *Lynn*[14,15] found another homogeneous system exhibiting concentration oscillations: the thermal decomposition of sodium dithionite.

In buffered (pH $\approx$ 4) aqueous solution, sodium dithionite decomposes above 50 °C according to the reaction:

$$2Na_2S_2O_4 + H_2O \rightarrow 2NaHSO_3 + Na_2S_2O_3$$

Experimental findings indicate an autocatalytic reaction step suspected by *Mason* and *Depoy*[16] to lie in the following two-step radical reaction:

$HSO_2^{\bullet}$	$+HSO_3^-$	$\rightarrow H_2S_2O_5$
$H_2S_2O_5$	$+HS_2O_4^-$	$\rightarrow 2HSO_3^{\bullet} + HS_2O_3^-$
$HSO_2^{\bullet} + HSO_3^{\bullet} + HS_2O_4^-$		$\rightarrow HS_2O_3^- + 2HSO_3^{\bullet}$

According to *Wayman* and *Lem*[17], $HSO_3^{\bullet}$ takes up an electron to form the reaction product HSO_3^-.

Interest in chemical oscillations was awoken primarily by the discovery of a highly impressive reproducible periodic reaction by *Belousov*[18] (1958). On attempting to oxidize citric acid by bromate in the presence of Ce^{4+}, he noticed that the yellow color of the Ce^{4+} ion in the homogeneous reaction mixture vanished and reappeared in a constant rhythm.

Credit goes mainly to *Zhabotinskii*[19,20] for recognizing the importance of this reaction for the understanding of periodic chemical and biological processes. In particular, he showed that the reactants could be modified and their oscillatory ability thereby considerably improved. Thus the citric acid can be replaced to advantage by other brominatable organic compounds, especially by malonic acid. *Zhabotinskii* also recognized that the Ce^{4+} ion serves as electron transfer agent and can be replaced by redox systems having a correspondingly high positive redox potential. The reactants of the "Belousov-Zhabotinskii reaction", currently the most thoroughly studied process of its kind, are a solution of malonic acid, potassium bromate, and cerium(IV) sulfate in 3 N sulfuric acid. After an induction period of about 10 min, extremely regular oscillation sets in at a frequency of about two periods per minute (at room temperature). They persist for about 15 to 30 min in a closed system, and can be maintained indefinitely in an open system with a constant reactant flux.

Table 1 lists the components of the Belousov-Zhabotinskii reaction. Potential organic brominatable components are compounds bearing a hydrogen readily substituted by bromine in the proximity of a carbonyl group. The redox potential of the electron transfer agent must exceed 0.9 V[21], and the

Table 1. Modifications of the Belousov-Zhabotinskii reaction. Overall process for the most thoroughly investigated variant:

$$2BrO_3^- + 3CH_2(COOH)_2 + 2H^+ \rightarrow 2BrCH(COOH)_2 + 3CO_2 + 4H_2O$$

Reducing agent	Oxidizing agent	Electron transfer agent	Acidic medium
Malonic acid	$KBrO_3$	Ce^{3+}/Ce^{4+}	H_2SO_4
Bromomalonic acid	KIO_3/H_2O_2	Mn^{2+}/Mn^{3+}	$HClO_4$
Citric acid		Ferroin/Ferriin [a]	
Malic acid		$Ru(bpy)_3^{2+}/Ru(bpy)_3^{3+}$ [a]	
Gallic acid		$Ru(phen)_3^{2+}/Ru(phen)_3^{3+}$ [a]	
Acetone			
Acetonedicarboxylic acid			
2,4-Pentanedione			
2,5-Hexanedione			

[a] Ferroin = $Fe(phen)_3^{2+}$; ferriin = $Fe(phen)_3^{3+}$; bpy = 2,2′-bipyridine; phen = 1,10-phenanthroline.

reaction medium must contain a strong acid. Moreover, bromination can be replaced by iodination with iodate/hydrogen peroxide[22]. The Belousov-Zhabotinskii reaction has not yet been completely elucidated[19-21,23-29].

At present some ten reactions of twelve reactants are under discussion. Six of the ten reaction steps are regarded as essential partial reactions, two of them being considered as constituting an autocatalytic process. There remain the following five reactions viewed as responsible for the oscillations in a narrower sense:

1) $BrO_3^- + Br^- + 2H^+ \rightarrow HBrO_2 + HOBr$
2) $HBrO_2 + Br^- + H^+ \rightarrow 2HOBr$
3) $BrO_3^- + HBrO_2 + 2Ce^{3+} + 3H^+ \rightarrow 2HBrO_2 + 2Ce^{4+} + H_2O$
4) $2HBrO_2 \rightarrow BrO_3^- + HOBr + H^+$
5) $nCe^{4+} + BrCH(COOH)_2 \rightarrow nCe^{3+} + Br^- +$ oxidation products

Reaction (3) is a stoichiometric autocatalytic reaction with respect to $HBrO_2$. It is assumed to proceed in two steps *via* the $BrO_2^{\bullet}$ radical.

$$BrO_3^- + HBrO_2 + H^+ \rightarrow 2BrO_2^{\bullet} + H_2O$$
$$2BrO_2^{\bullet} + 2Ce^{3+} + 2H^+ \rightarrow 2HBrO_2 + 2Ce^{4+}$$
$$\overline{BrO_3^- + HBrO_2 + 2Ce^{3+} + 3H^+ \rightarrow 2HBrO_2 + 2Ce^{4+} + H_2O}$$

Assuming the protonations to be very fast, all the steps of the reactions given are of 2nd order.

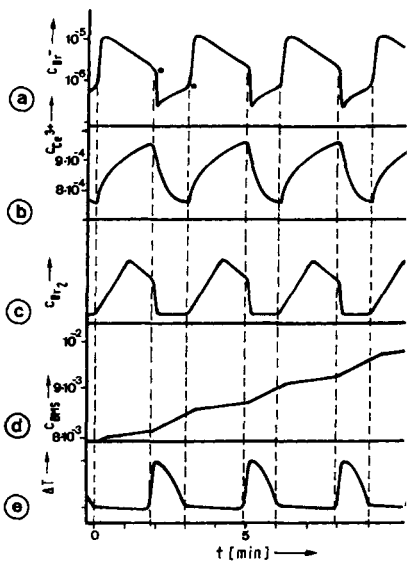


Fig. 4. Belousov-Zhabotinskii oscillation: bromination of malonic acid with bromate in the presence of Ce^{4+}. a) Br^- concentration [24]; b) Ce^{3+} concentration [79]; c) bromine concentration (spectroscopic measurement by *W. Geiseler* [79, 81]; d) concentration of bromomalonic acid (BMA) in a closed system (according to [80]); e) temperature oscillation in a heat-flow calorimeter (measurements by *W. Geiseler*) [79, 81]. The synchronization lines refer to the instability points of bromide concentration. Concentrations are given in mol l^{-1}.

The oscillation process is presented in synoptic manner with regard to the most important analytically accessible variables (Br^-, Ce^{3+}/Ce^{4+}, Br_2, bromomalonic acid, and temperature) in Figure 4.

The oscillations consist in a kind of flip-flop alternation between two reaction states: one in which Ce^{4+} is reduced and another in which Ce^{3+} is oxidized. The bromide concentration is relatively high in the reducing phase, and extremely low in the oxidizing phase. Formation of bromomalonic acid is more pronounced in the reducing phase than in the oxidizing phase. The same applies to the evolution of heat. Bromine appears briefly during the transition from the oxidizing to the reducing phase.

Noyes et al.[30,31] formulate the reaction sequence as follows: In the Belousov-Zhabotinskii reaction, bromination of malonic acid can, in principle, proceed *via* two mutually exclusive pathways.

a) Pathway involving reduction of Ce^{4+} to Ce^{3+} in the presence of bromide ion:

$$BrO_3^- + 2Br^- + 3H^+ \rightarrow 3HOBr$$
$$HOBr + CH_2(COOH)_2 \rightarrow BrCH(COOH)_2 + H_2O$$

Bromomalonic acid subsequently reduces the Ce^{4+} present to Ce^{3+}, thereby decomposing to CO_2 and bromide:

$$BrCH(COOH)_2 + 4Ce^{4+} + 2H_2O \rightarrow Br^- + 4Ce^{3+} + HCOOH + 2CO_2 + 5H^+$$
$$HCOOH + HOBr \rightarrow Br^- + CO_2 + H^+ + H_2O$$

The overall process in the reducing phase is:

$$BrO_3^- + 2CH_2(COOH)_2 + 4Ce^{4+} \rightarrow BrCH(COOH)_2 + 4Ce^{3+} + 3CO_2 + 3H^+ + H_2O$$

b) Pathway involving oxidation of Ce^{3+} to Ce^{4+} in the absence of bromide ion:

The oxidizing species is now bromate, which oxidizes Ce^{3+} and is itself reduced to HOBr. The latter then brominates malonic acid:

$$BrO_3^- + 4Ce^{3+} + CH_2(COOH)_2 + 5H^+ \rightarrow BrCH(COOH)_2 + 4Ce^{4+} + 3H_2O$$

Together, pathways a) and b) comprise the overall oscillation reaction:

$$2BrO_3^- + 3CH_2(COOH)_2 + 2H^+ \rightarrow 2BrCH(COOH)_2 + 3CO_2 + 4H_2O$$

The presence of Br^- thus determines which of the two bromination pathways is feasible. Each individual reaction pathway is assumed to proceed *via* intermediates not included in the above partial equations. Bromous acid ($HBrO_2$) is accordingly assigned a crucial role.

In the reducing phase (pathway a) the following intermediate steps are assumed to occur in the first equation:

$$BrO_3^- + Br^- + 2H^+ \rightarrow HBrO_2 + HOBr$$
$$HBrO_2 + Br^- + H^+ \rightarrow 2HOBr$$
$$\overline{BrO_3 + 2Br^- + 3H^+ \rightarrow 3HOBr}$$

In the oxidizing phase (pathway b), the reaction proceeds *via* the above mentioned and formulated autocatalytic step involving $HBrO_2$ (reaction 3). This species disproportionates to bromate and HOBr, which subsequently brominates malonic acid:

$$2BrO_3^- + 2HBrO_2 + 4Ce^{3+} + 6H^+ \rightarrow 4HBrO_2 + 4Ce^{4+} + 2H_2O$$
$$2HBrO_2 \rightarrow BrO_3^- + HOBr + H^+$$

$$BrO_3^- + 4Ce^{3+} + 5H^+ \rightarrow HOBr + 4Ce^{4+} + 2H_2O$$
$$HOBr + CH_2(COOH)_2 \rightarrow BrCH(COOH)_2 + H_2O$$

$$BrO_3^- + 4Ce^{3+} + CH_2(COOH)_2 + 5H^+ \rightarrow BrCH(COOH)_2 + 4Ce^{4+} + 3H_2O$$

This is the equation of pathway b).

Numerous experimental results suggest that the formulations presented here provide an essentially correct description of the individual reaction steps. However, various questions remain open, particularly in connection with the actual origin of the oscillations. A system of four simultaneous differential equations derived from the above formulations, called the "Oregonator"[25] by analogy with the "Brusselator" and which also has oscillatory solutions, takes the following form:

$$A + Y \rightarrow X + P$$
$$X + Y \rightarrow 2P$$
$$A + X \rightarrow 2X + Z$$
$$2X \rightarrow P + A$$
$$Z \rightarrow \frac{PY}{a+P} - \frac{P^2}{a+P}$$

$A = BrO_3^-$; $X = HBrO_2$; $Y = Br^-$; $Z = 2Ce^{4+}$; P = bromomalonic acid. A detailed discussion of the resulting differential equations will be found in the specialist literature[18-33].

2.1.2. Thermochemical Oscillations in Gas Reactions

Periodic reaction courses are also observed in a number of gas reactions. A typical example is shown in Figure 5. As with the periodic reactions occurring in solution, interfacial structures play no part.

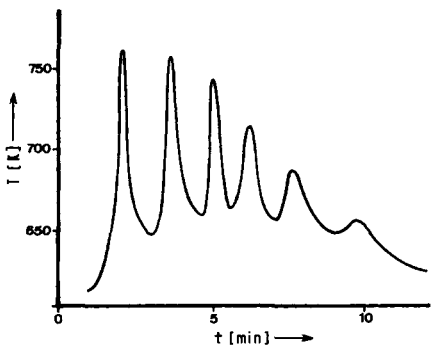


Fig. 5. Temperature oscillation in the thermochemical oxidation of propane in oxygen (C_3H_8: 50 mol %. P: 75 kNm^{-2}) (according to [37]).

On oxidation of hydrocarbons in mixtures with oxygen, "cold flames" occur at relatively low temperatures ($\approx$400 °C)[34-38]. This kind of combustion frequently proceeds with rhythmic emission of pale blue light and periodic evolution of heat.

Oscillations are also observed on combustion of hydrogen sulfide[39] and of carbon monoxide[40-42] in oxygen. The oscillations of phosphorus vapor in contact with oxygen described by *Rayleigh*[43, 44] may also belong to this class of periodic chemical reactions.

The kinetics of thermochemical oscillations is still poorly understood. Once again, however, autocatalytic processes and chemical feedback are known to play an important part. In gas phase reactions, autocatalysis frequently involves branched chain reactions which can occur both in the formation and in the decomposition of intermediates. Gas reactions generally span wide ranges of temperature. Under these conditions, the temperature dependence of the rate constants leads to marked non-linearity and non-stoichiometric coupling between all the participating reactions.

Two oscillating thermochemical reactions have recently been studied in particular detail, *viz.* the oscillations of cold flames of propane at about 330 °C (Fig. 5)[37] and the thermochemical oscillations of carbon monoxide in oxygen at 600 °C[41, 42]. The kinetics of these reactions is apparently very complicated. The most important reactions involve short-lived radicals which are very difficult or impossible to detect analytically. In the oscillatory combustion of CO[42], 18 reactions of 12 reactants are under consideration—eight simultaneous kinetic differential equations are obtained. An incomprehensible variety of material and thermal coupling modes results.

2.2. Oscillations in Heterogeneous Systems

This Section is concerned with systems whose oscillatory behavior is strictly linked with interfacial structures. Such is the case when one of the oscillatory variables is electrical in nature.

Oscillations in electrochemical systems concern changes of state involving local currents between regions in different electrochemical states. Such local currents can occur in closed circuits only at interfaces present at electrodes and ion membranes.

The treatment of heterogeneous catalytic reactions requires a knowledge of the structure of the interface because reaction-dependent interfacial states are crucial to the occurrence of periodicity.

2.2.1. Electrochemical Oscillations

Periodic electrode processes are the longest known of all chemical oscillations. As long ago as 1828, such reactions were reported by *Fechner*[45]. Around the turn of the century, *Ostwald*[46, 47] engaged in a thorough study of the oscillations of potential and corrosion of chromium in hydrochloric acid and of iron in nitric acid. He was the first to recognize a surprisingly complete kinetic analogy between electrochemical and electrophysiological oscillations[48] which is not limited merely to the actual oscillations but extends over the entire phenomenology of nervous stimulation. This was demonstrated by very impressive analogy experiments performed in the 1920's and 1930's by *Lillie*[49, 50].

Systematic physicochemical research into chemical oscillations did not begin until about 1940 with *Bonhoeffer*'s fundamental studies[51-53] on the "Ostwald-Lillie nerve model" and "Periodic chemical reactions".

We are now familiar with a large number of electrochemical oscillations. Most of them are observed at electrodes on which

anodic or cathodic surface layers can form. Such electrodes generally possess non-monotonic current-voltage curves, which arise because surface layer formation or removal sets in at a particular electrode voltage.

The current usually changes abruptly and the current-voltage curve shows the N-shaped course characteristic of surface layer electrodes[54, 55]. With suitable external circuitry, *i.e.* with a suitable position of the load line, the possibility of bistability arises which is one of the prerequisites for the occurrence of oscillations.

sponds to positive feedback and the coupled regeneration process to negative feedback.

There is also another kind of electrode oscillation[56] which differs in its temporal course and frequency from passivation-activation oscillation, and occurs only under potentiostatic conditions.

These oscillations are usually associated with electropolishing effects. Their frequency is relatively high, lying between 80 and 4000 Hz (Fig. 7). They give rise to a flickering effect which can readily be observed under a microscope. At certain

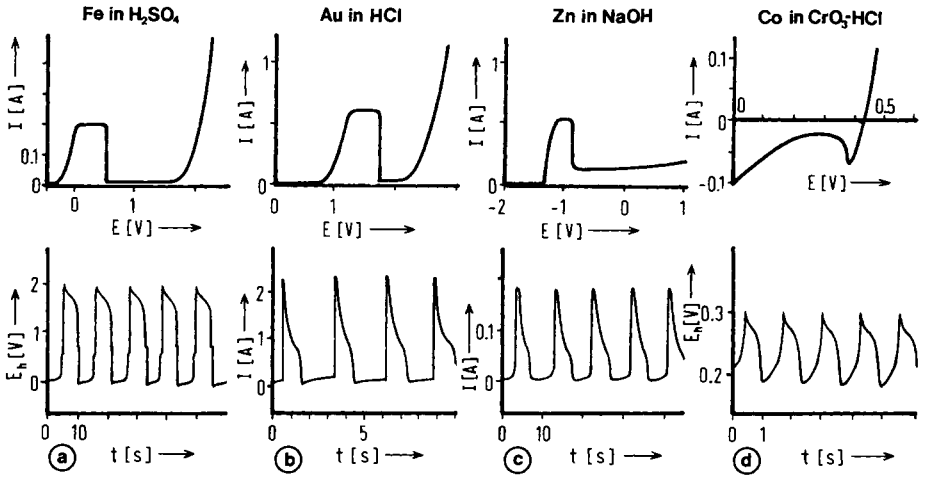


Fig. 6. Examples of electrochemical oscillations. Upper row, non-monotonic current-voltage curves; lower row, galvanostatic (I = const.) or potentiostatic (E = const.) oscillations. a) Galvanostatic voltage oscillation at iron in 3.16 N H_2SO_4 + 0.04 N HCl [56, 59]; b) potentiostatic current oscillation at gold in 4 N HCl at $E_h = +1.75$ V [82, 54]; c) potentiostatic current oscillation at zinc in 4 N NaOH at $E_h = -1.1$ V [82, 83]; d) spontaneous ($I = 0$) voltage oscillation at cobalt in 0.4 M CrO_3 + 1 N HCl [82, 84, 85].

Some typical examples of non-monotonic current-voltage curves and oscillograms recorded for surface layer electrodes are presented in Figure 6.

Periodicity at these electrodes arises because the voltage-independent passivation-activation process is coupled with a further process which, after a brief lapse of time, reverses the change of state resulting from passivation or activation. This mechanism will be examined more thoroughly in Section 3.3. It will also be shown that passivation-activation corre-

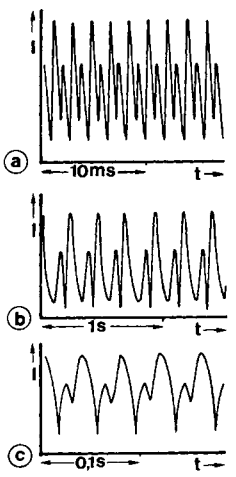


Fig. 7. Fast potentiostatic "flicker" oscillations [56, 83] a) at zinc in 1 N H_2SO_4 at $E_h = -0.29$ V; b) at iron in 1 N H_2SO_4 at $E_h = +0.3$ V; c) at silver in 0.7 N KCN at $E_h = +0.53$ V.

electrode potentials the flickering shows some degree of synchronization and interference colors appear, *e.g.* on zinc in sulfuric acid. The mechanism of these oscillations is not yet completely understood. It seems reasonable to invoke dynamic dissipative structures which synchronize at certain potentials and then become recognizable in the external current.

2.2.2. Oscillations in Membrane Systems

Electrochemical oscillations can occur at ion-conducting membranes in the same way as at electron-conducting electrodes. The electrophysiological oscillations of nerve, muscle, and sensory organ cells of living organisms are known to take place at such membranes. *Teorell*'s observation[57, 58] that even very simple porous ion exchange membranes exhibit oscillatory behavior under constant external conditions attracted considerable interest in this context.

The "Teorell membrane oscillator" has since been studied in great detail with respect to its ion-transport kinetics. It consists of a highly porous membrane of ion exchange material separating two compartments, which contain sodium chloride solutions of different concentrations, and carrying a constant electrical current (Fig. 8a). The essential oscillatory variables are the membrane potential E, determined by the membrane resistance, and the hydrostatic pressure P which is set up as a consequence of the hydrodynamic and electroosmotic volume flow V between the compartments on the two sides of the membrane.

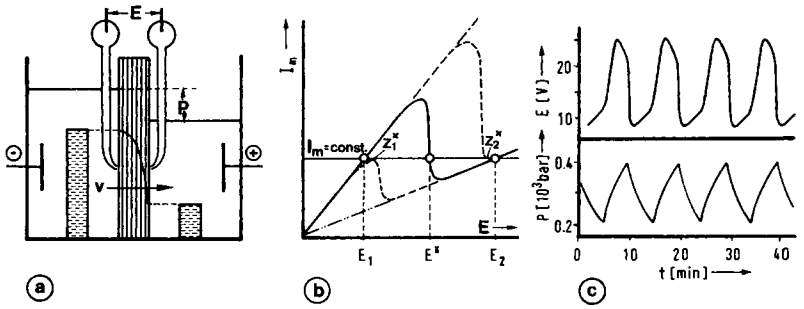


Fig. 8. The Teorell membrane oscillator. a) Experimental set-up; b) current-voltage curve [59]; c) oscillations of voltage and pressure [58, 59].

The voltage and pressure oscillations occurring in the Teorell oscillator are shown in Figure 8c. The membrane may consist of unglazed porcelain, porous sintered glass, porous plastic, or pressed powders of quartz, metal oxides, or organic ion-exchanger material.

Oscillations occur when the sign of the fixed ion charge, the direction of the electric current, and the concentration gradient of the salt solutions can be suitably combined[59, 60]. Under such conditions the membrane has a non-monotonic current-voltage curve (Fig. 8b) as a result of reversal of the direction of flux of the salt solution at a particular membrane potential and the membrane resistance jumps to the value corresponding to the modified influx of salt solution.

In Figure 8b the load line I_m=const. intersects the non-monotonic membrane characteristic at three positions: hence three steady states occur, of which the middle one is unstable and the two outside ones are stable. The volume flux, which is driven antagonistically by the pressure (P) and potential (E), shifts the critical flux reversal potential E^x in the same way as the hydrostatic pressure changes with the volume flux. The system becomes unstable at the limits shown in Figure 8b, the volume flux reverses, and the potential jumps onto the other branch of the membrane characteristic. In this way the state of the system alternates periodically between the two points of instability (Z_1^x and Z_2^x). The oscillations thus represent spontaneous alternating initiation of changes of state of the membrane which are triggered by the hydrostatic pressure, which itself depends upon the particular membrane state. The Teorell membrane oscillator convincingly shows how instability and kinetic coupling lead to oscillation. The existence of the non-monotonic characteristic is a consequence of positive feedback whereas the hydrostatic pressure effects a negative feedback.

From a chemical and structural standpoint, two other artificial excitable membranes resemble the oscillatory nerve membrane even more closely. These are the bimolecular lipid membranes containing antibiotics, which were developed by *Müller* and *Rudin*[61] (Fig. 9a), and the polyelectrolyte membranes produced and studied by *Shashoua*[62, 63] (Fig. 9b).

Both kinds of membranes are capable of oscillation and exhibit electrophysiological excitation phenomena. Like the Teorell membrane, they possess non-monotonic current-voltage curves. They are therefore bistable and have unstable states. In the case of the lipid membranes this behavior is caused by a pore-formation mechanism of the incorporated antibiotic (*e.g.* alamethicin). *Shashoua*[62] assumes that a mechanism of cation-anion contact analogous to the p-n junction in semiconductors operates in the polyelectrolyte membrane.

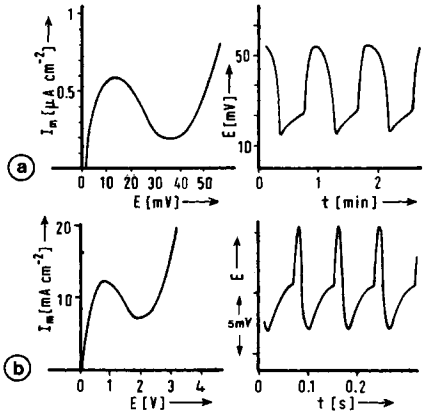


Fig. 9. Oscillations at biochemical membranes. a) Müller-Rudin oscillator [61]; left, current-voltage curve; right, galvanostatic voltage oscillation at a phosphatidylcholine double-layer membrane containing 10^{-7} g ml^{-1} of alamethicin and 10^{-5} g ml^{-1} of salmin. I = 3.2 μA cm^{-2} (according to experiments by *G. Boheim* [86]). b) Shashoua oscillator [62]; left, current-voltage curve of a polyglutamate-Ca^{2+} ion exchange membrane; right, voltage oscillation at a methacrylate-acrylic acid-Ca^{2+} membrane.

2.2.3. Chemical Oscillations in Systems with Heterogeneous Catalysts

Oscillations in heterogeneous systems include the periodic reactions observed in contact catalytic reactors. That unstable reaction states occur in exothermic reactions of gases at heterogeneous catalysts follows from theoretical studies by *Wagner*[64], *van Heerden*[65], and *Frank-Kamenetzkii*[66].

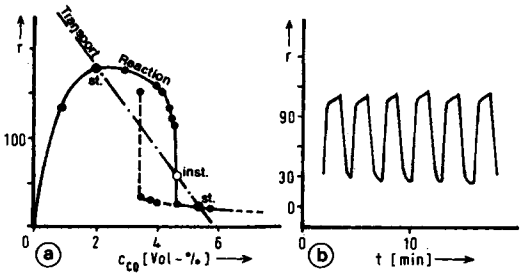


Fig. 10. Oscillation in the oxidation of CO by air at a platinum-Al_2O_3 contact catalyst. a) Reaction-transport characteristic; r is the relative rate constant in ppm CO_2 in exhaust gas; the broken curve indicates hysteresis on reverse order of measurement; b) oscillation at a single grain of catalyst; r refers to the CO_2 concentration in ppm (according to [67]).

The most exhaustive experimental studies have been performed on the oscillatory behavior of the oxidation of carbon

monoxide and of hydrogen by atmospheric oxygen over platinum-alumina catalysts[67]. Figure 10 shows an example of such an oscillation in a heterogeneous reaction taken from the work of *Wicke et al.*[67]. As in electrochemical oscillatory systems, non-monotonic reaction characteristics are found once again. There exist an unstable reaction state and two stable steady states.

Reactors of this kind are thus also bistable in the non-oscillatory state[67, 68], and the oscillations are periodic alternations between two quasi-stable reaction states. Two possible feedback modes exist in heterogeneously catalyzed reactions: 1) by the non-linear temperature dependence of catalyzed exothermic reactions and 2) by kinetic action of the reaction products on the effectiveness of the catalyst, for example by changing the surface coverage. The first case is an example of positive feedback and the second case one of negative feedback. Both kinds of feedback can lead to oscillations.

2.3. Oscillations in Biological Systems

Rhythmic processes are characteristic of living organisms. Elementary oscillatory phenomena were recognized and studied very early in electrophysiology, and hence much of the terminology of oscillation and excitation kinetics comes from neurophysiology.

2.3.1. Electrophysiological Oscillations

Oscillations of cells of nerve and muscle tissue and of sensory organs are periodic excitation processes at ionic membranes (Fig. 11) which possess a specific, potential-dependent selectivity for sodium and potassium ions. As a result, the nerve membrane exhibits a non-monotonic current-voltage curve like that of non-living ion membranes capable of oscillation and therefore possesses bistability and instability. The nature of the second or further kinetic variables has not yet been

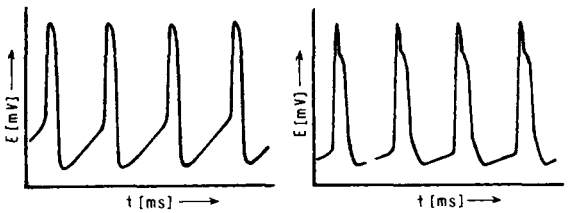


Fig. 11. Oscillations at biological membranes. a) At an octopus nerve fiber [87]; b) at a single heart muscle fiber [88].

unequivocally established for biological membranes capable of oscillation. Divalent ions such as the calcium ion might play an essential role.

2.3.2. Enzymatic Oscillations

Purely chemical oscillations have been known to occur in living organisms since 1955, when *Wilson* and *Calvin*[69] first observed such processes in the dark reaction of photosynthesis. Meanwhile, oscillatory reaction courses have been detected in numerous areas of biochemistry, in cell respiration, in carbohydrate metabolism, in enzyme synthesis, mitosis, morphogenesis, regeneration of damaged cells, and other essential life processes. The common feature of all these oscillations is their enzymatic nature.

Enzymatic reactions are known to be catalytic processes in which the enzyme is regenerated in a cyclic manner. It would appear that these reaction cycles do not always occur at a steady rate but rather in rhythmic waves. The reason is clearly seen to lie in the frequent substrate- or product-dependence of the enzyme effectiveness. Chemical feedback is then possible and the condition for an oscillatory reaction course is thus fulfilled.

In 1957, *Duysens* and *Amesz*[70] observed that glycolysis, *i.e.* the anaerobic degradation of glucose in living cells to pyruvate, follows a periodic course. The oscillatory glycolysis system can be isolated from cellular material by extraction and studied *in vitro*[71, 72]. In homogeneous phase this oscillation has the advantage that it can be relatively easily monitored by observing the fluorescence of the NADH participating in the reaction (Fig. 12).

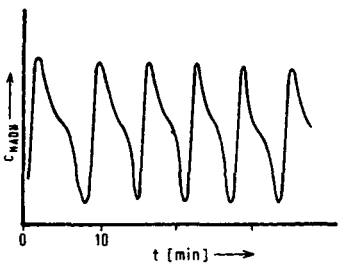


Fig. 12. Oscillation in glycolysis. The reduced form of nicotinamide dinucleotide (NADH) participating in glycolysis exhibits readily measurable fluorescence permitting fluorimetric monitoring of the oscillation (according to [89]).

Although the mechanism of oscillation of glycolysis has not yet been fully elucidated, a number of important chemical and kinetic aspects of this interesting process are known.

Phosphofructokinase, an allosteric enzyme, seems to play a critical role. This enzyme is inhibited by one of its substrates, ATP, and activated by its products, ADP and fructose 1,6-diphosphate. The chemical feedback necessary for oscillation is thus ensured[73].

Yamazaki, *Yokota*, and *Nakajima*[74, 75] found the peroxidase oxidation of NADH by atmospheric oxygen to be the first periodic enzyme reaction which can be maintained indefinitely in a thermodynamically open system.

2.4. Non-oscillatory Phenomena of Systems Capable of Oscillation

The special kinetic situation existing in oscillatory systems, due primarily to non-linear relationships, to kinetic coupling, and to instability, leads to typical temporal behavior when oscillations no longer occur under modified conditions. Non-oscillatory phenomena of this kind can provide valuable clues as to the nature of individual processes involved in the origin of oscillations.

The surprising degree of similarity in the behavior of systems capable of oscillation is apparent from the survey of their phenomenology presented in Figure 13[76, 77]; this survey could be readily extended. It also includes a very simple electronic semiconductor system (neurodyn model) which was developed on the basis of common kinetic features. It consists of a tunnel diode (TD) with a non-monotonic current-voltage curve and a NTC thermistor with the properties of coupled

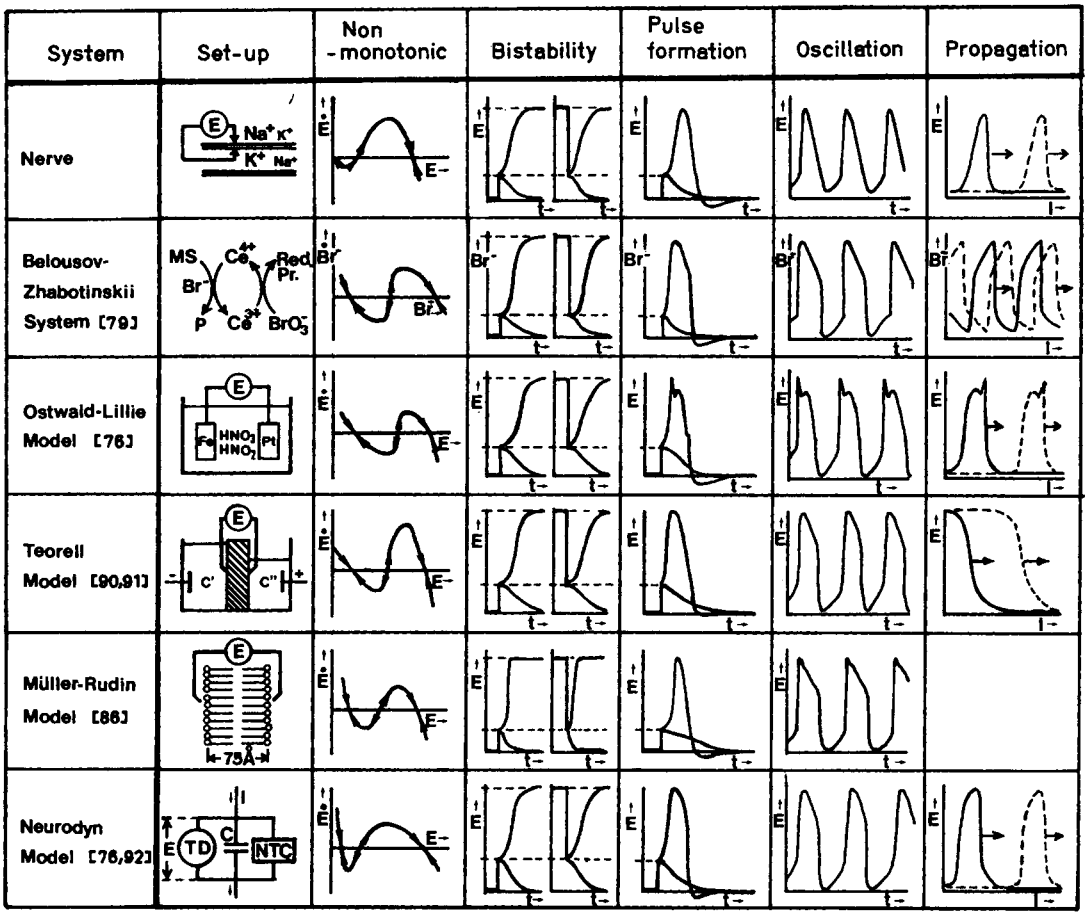


Fig. 13. Phenomenological analogy between chemical and physicochemical oscillatory systems. MA, malonic acid; P, product; Red. Pr., reduced products; $\dot{E}=dE/dt$; $\dot{B}r^-=dBr^-/dt$. The right- and left-hand curves in the column headed "Bistability" refer, respectively, to excitation from the lower to the upper and from the upper to the lower stable steady state; the broken lines indicate the position of the steady states.

regeneration. The entire phenomenology of excitable and oscillatory systems can be simulated with this model[76,92].

Systems no longer in oscillation usually still possess bistability (see Fig. 2a). Interconversion of the two stable reaction states, which can be triggered by external perturbation, obeys the so-called "all-or-none law" and therefore has threshold character. Typically, such transitions between states propagate spontaneously throughout the system once induced at a point by local transport processes ("local fluxes") set up at the boundaries between regions in different reaction states resulting from the bistability of the system (cf. Fig. 15).

In some cases, the triggered system may return to the original state in a spontaneous regeneration process coupled with the triggering reaction. We then have the phenomenon of triggered reaction pulses (for example, action potentials of nerves), which likewise propagate spontaneously.

The ubiquitous phenomena of overshoot (Fig. 2b), refractarity, and accommodation, which are all consequences of coupled regeneration, will not be considered in this article. The individual terms mean threshold alteration under superthreshold conditions (refractarity) or subthreshold conditions (accommodation).

3. Theory of Chemical Oscillations

The phenomenology of the oscillatory systems shows that certain thermodynamic and kinetic conditions must be fulfilled for periodic behavior to occur. The most important conditions will now be briefly summarized:

a) Oscillatory processes concern temporal changes of state which take place remote from thermodynamic equilibrium. They occur as temporally unlimited phenomena only in thermodynamically open systems, *i.e.* systems with a material flux.

b) Several kinetic variables participate in the periodic process. It follows from the phase shifts recognizable in the oscillograms that the variables are not directly interdependent but merely coupled with one another kinetically, *i.e.* they can be set independently but nevertheless mutually affect each other's rates of change. Hence no direct functions exist of the kind $y=f(x,...)$ but only a set of simultaneous differential equations of the kind:

$$\frac{dx}{dt}=f_x(x,y,...)$$

$$\frac{dy}{dt}=f_y(x,y,...)$$

. . .
. . .
. . .

c) Oscillatory systems are non-linear in their kinetic relationships, and they contain autocatalytic or autoinhibitory processes.

3.1. Multivariable Kinetics of Chemical Oscillations

Periodic chemical reactions are thus seen to be understandable only on the basis of multivariable kinetics, describable only in terms of sets of simultaneous differential equations.

Since two variables already suffice for a description of oscillations we shall limit the following brief treatment of multivariable kinetics to cases involving two variables:

The system under consideration will be described by two simultaneous differential equations in the kinetic variables x and y:

$$\frac{dx}{dt} = f_x(x,y);$$

$$\frac{dy}{dt} = f_y(x,y)$$

Elimination of the common term t gives:

$$\frac{\frac{dy}{dt}}{\frac{dx}{dt}} = \frac{dy}{dx} = \frac{f_y(x,y)}{f_x(x,y)}$$

i.e. an expression describing the direction in which the state of the system changes at each point x, y in an x/y coordinate system. A time-free "state portrait" (phase plane) of the system described by the kinetic differential equations is obtained. The reaction vectors thus given for each point form continuous trajectories which can be shown to intersect only at discrete points. The intersections of the trajectories shown are the steady states of the system. They may be stable or unstable, depending upon whether the temporal changes along the trajectories are directed into or out of the singular point. Figure 14 shows the portraits of the surroundings of various kinds of singular points occurring in kinetic systems. They may be "nodes", "foci", or "saddle points". The lines which

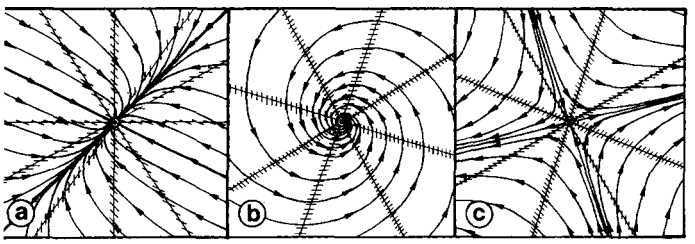


Fig. 14. Trajectories and isoclines surrounding singular points (=steady states) in the two-dimensional portrait of state. a) Stable nodes; b) stable foci; c) saddle point.

join states having the same direction of their trajectories in the state portrait are called isoclines.

The portraits of non-linear coupled systems of particular interest in the present article are shown in Figure 15. The cases shown are those of bistability, pulse formation, and oscillation, which are readily interconvertible by variation of the coefficients in the two kinetic differential equations.

Systems exhibiting bistability (Fig. 15a) possess three singular points, of which the middle one is a saddle point and the other two nodes or foci.

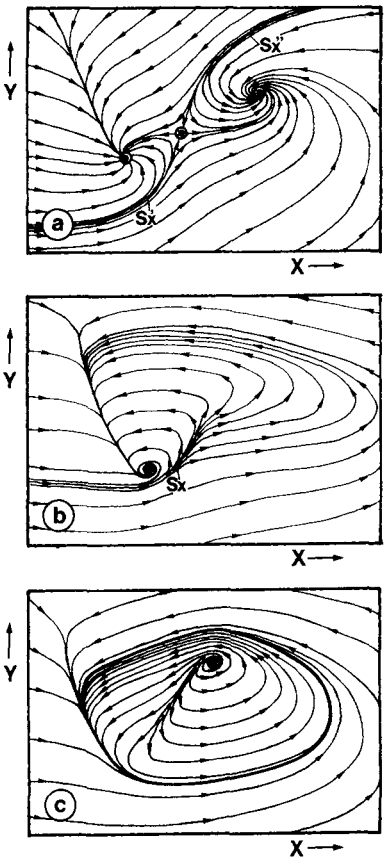


Fig. 15. State portraits of coupled systems. a) Bistability; b) excitable pulse formation (monostability); c) oscillation (astability). S_x = separatrix. The portraits correspond to the behavior of the neurodyn oscillator shown in the bottom row of Fig. 13 (experiments by *E. Lammel* [93]).

In the case of pulse formation ("monostability") (Fig. 15b) there exists only one stable node or focus and a "separatrix" (S_x), which determines whether the system returns directly (subthreshold stimulus) or *via* an extended route to the stable singular state (superthreshold stimulus).

In the oscillatory case (Fig. 15c) there arises a boundary cycle into which all the trajectories approach, whether they come from without or within. The system moves indefinitely on this closed loop, and its projections onto the x axis and the y axis show the oscillations of these two variables. They are seen have a phase lag of about one quarter of the entire cycle. In simultaneously recorded oscillograms one variable is seen to undergo maximum change when the other exhibits minimum change at its point of inversion. The kinetic situation in chemical oscillations is thus completely analogous to those known in mechanical and electrical oscillatory systems.

It is seen in Figure 15c that oscillatory systems in the interior of the boundary cycle contain a singular state which is an unstable focus.

In order to assess the behavior of systems including two kinetic variables, great importance attaches to the analysis of the isoclines (Fig. 14). Like the trajectories they intersect only at singular points; unlike the trajectories, however, which are generally no longer calculable in elementary form by integration, the isoclines are usually obtainable as relatively simple functions of x and y from the relation

$$f_y(x,y) - \sigma f_x(x,y) = 0$$

where $\sigma = dy/dx = \text{const.}$ refers to the trajectory slope characterizing the relevant isocline.

By means of the isoclines, the trajectories or paths of state can be approximately shown in the portrait of state and the properties of the singular states determined; in particular, it can be deduced from the position and shape of the isoclines whether a given system of simultaneous differential equations possesses oscillatory solutions or not.

3.2. The Problem of Stoichiometric Chemical Oscillations

The facts that chemical oscillations have hitherto always been discovered merely by chance and that no oscillatory system has yet been "synthesized" from known reactions, together with the failure to completely elucidate even one of the known oscillations, underline the difficulties besetting the formulation of periodic reactions with stoichiometric reaction equations.

The question then arises as to the possibility of realistic stoichiometric reactions being able to meet the known requirements for oscillation.

Only systems of two kinetic variables will be considered, and the following limitations apply:

a) The realistic range of existence lies in the first quadrant of the x/y coordinate system since x and y are concentrations and cannot assume negative values.

b) The isoclines must intersect at least once in the first quadrant in order that at least one steady state exists there.

c) The chemical reaction must be of second order or lower since reactions of higher order are unlikely or unrealistic.

Bearing these limitations in mind, there remain surprisingly few kinds of reactions which can be considered in setting up stoichiometric reaction mechanisms. Only five normal non-catalytic and two autocatalytic reactions are left in the discussion:

a) Uncoupled reactions (containing only one variable):

$A + X \rightarrow P$
$X + X \rightarrow P$
$A + X \rightarrow 2X$ (autocatalytic)

b) Coupled reactions (containing both variables):

$A + X \rightarrow Y$
$X + X \rightarrow Y$
$X + Y \rightarrow P$
$X + Y \rightarrow 2X$ (autocatalytic with respect to X)

These seven kinds of equations yield seven types of kinetic terms which can occur in the kinetic equations; it should be remembered that X and Y are interchangeable.

$$\frac{dx}{dt} = -kx \qquad \frac{dy}{dt} = +kx$$

$$\frac{dx}{dt} = -2kx^2 \qquad \frac{dy}{dt} = +kx^2$$

$$\frac{dx}{dt} = +kx \text{ (autocatalytic)} \qquad \frac{dx}{dt} = -kxy$$

$$\frac{dx}{dt} = +kxy \text{ (autocatalytic)}$$

Thus only linear and quadratic terms (x^2, y^2, xy) appear. Under these conditions the isoclines are always second order curves, *i.e.* conic sections; for the above terms they are hyperbolae, parabolae, and straight lines.

Taking into account the permissible kinetic terms, isocline analysis provides valuable information about the behavior of stoichiometric systems.

a) If the kinetic equations are linear and do not include an autocatalytic process, only one singular state occurs which is always a stable node in the first quadrant.

b) If the xy term is also present, the singular state can also be a focus, *i.e.* attenuated oscillations become possible.

c) If one of the linear terms is autocatalytic ($dx/dt = +kx$), then two singular states can occur in the first quadrant, of which one is a stable node and the other a saddle point, *i.e.* the system is excitable.

d) If quadratic terms are also present, three singular states can form in the first quadrant; the middle one is a saddle point and the others stable nodes. Bistability thus becomes possible[94].

e) Indefinite oscillations are *not* possible with the linear and quadratic terms given above.

If the choice of reactions is limited to stoichiometric ones, oscillations only become possible if terms of higher order (>2) are present in the kinetic equations.

In this context, the reader is reminded that, of the mathematical models of stoichiometric oscillations mentioned in Section 2.1.1, the Brusselator[12,13] includes a trimolecular reaction and the Oregonator[31] more than two kinetic variables and a non-stoichiometric coefficient ($P/(a+P)$).

A further realistic possibility for the generation of oscillations is provided by the presence of non-stoichiometric coupling processes, such as occur in chain branching and enzymatic reactions.

3.3. The Feedback Concept of Chemical Oscillations

The occurrence of unattenuated oscillations in electrical circuits and control loops as a consequence of feedback effects is a well known fact. Application of this concept to chemical reactions is unfamiliar since circuits and loops are not so immediately obvious. However, on closer study of chemical and physicochemical oscillation a very close analogy is seen to exist.

Feedback occurs when a process acts kinetically upon itself. It therefore consists basically in a closed chain of action. Such a cycle can arise in two ways:

a) If the output of a transmission system acts upon the input of the same system then we have a situation in which an "effect" is influencing its own "cause". Depending upon whether self-enhancement or self-inhibition occurs the phenomenons is described as positive or negative feedback, respective-

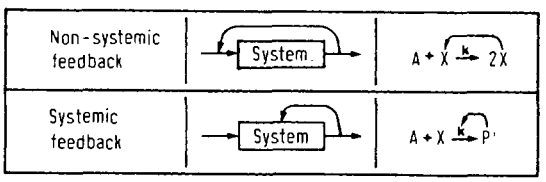


Fig. 16. "Non-systemic" and "systemic" feedback in chemical systems.

ly. The chemical analogy is stoichiometric autocatalysis (Fig. 16, top) in which the reaction product is also a reactant. This form of feedback has no effect upon the properties of the transmission system or upon the rate constant of the reaction. It is therefore designated "non-systemic" feedback.

b) Many feedback mechanisms act not upon the input but instead upon the transmission system itself. The kinetic analog is a reaction in which the reaction product influences the rate constant (Fig. 16, bottom). Owing to its action upon the properties of the system, this kind of feedback will be termed "systemic" feedback. It is the commonest kind of kinetic coupling in heterogeneous systems, *e.g.* at electrodes, contact catalysts, and membranes. It can arise in homogeneous systems, *e.g.* as a result of the markedly non-linear temperature dependence of the rate constants in thermochemical reactions, and in enzymatic systems, *e.g.* owing to the dependence of the catalytic activity of allosteric enzymes upon their products or substrates.

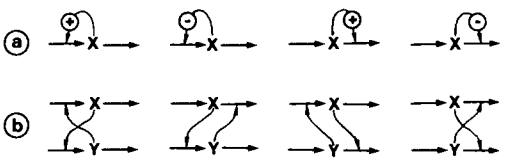


Fig. 17. Possible coupling modes in simply coupled chemical systems. a) Intrinsic coupling (autocatalysis ⊕, autoinhibition ⊖); b) cross-coupling (cross-catalysis, cross-inhibition).

Systemic feedback is usually non-stoichiometric (non-linear) and thus much more favorable to oscillations than stoichiometric non-systemic feedback which is linear, being restricted to bimolecular reactions.

In open systems, autocatalytic and autoinhibitory reactions can produce positive or negative feedback, depending upon whether the self-coupling affects the formation or consumption reaction of the coupled component. Four cases can occur (Fig. 17a), of which the first and last lead to positive feedback and the two middle ones to negative feedback.

Non-systemic or systemic coupling can also occur in kinetic interactions between simultaneous reactions. Feedback then occurs by "cross-catalysis", a concept introduced into the kinetics of chemical oscillations as long ago as 1948 by *Bonhoeffer*[52].

Once again there are four possible coupling modes which can lead to positive or negative feedback depending upon the direction of action of the individual couplings (Fig. 17b).

With regard to the occurrence of oscillation, interest is focused mainly on the kinetic behavior of chemical systems with positive and negative feedback. This will be considered with the aid of Fig. 18:

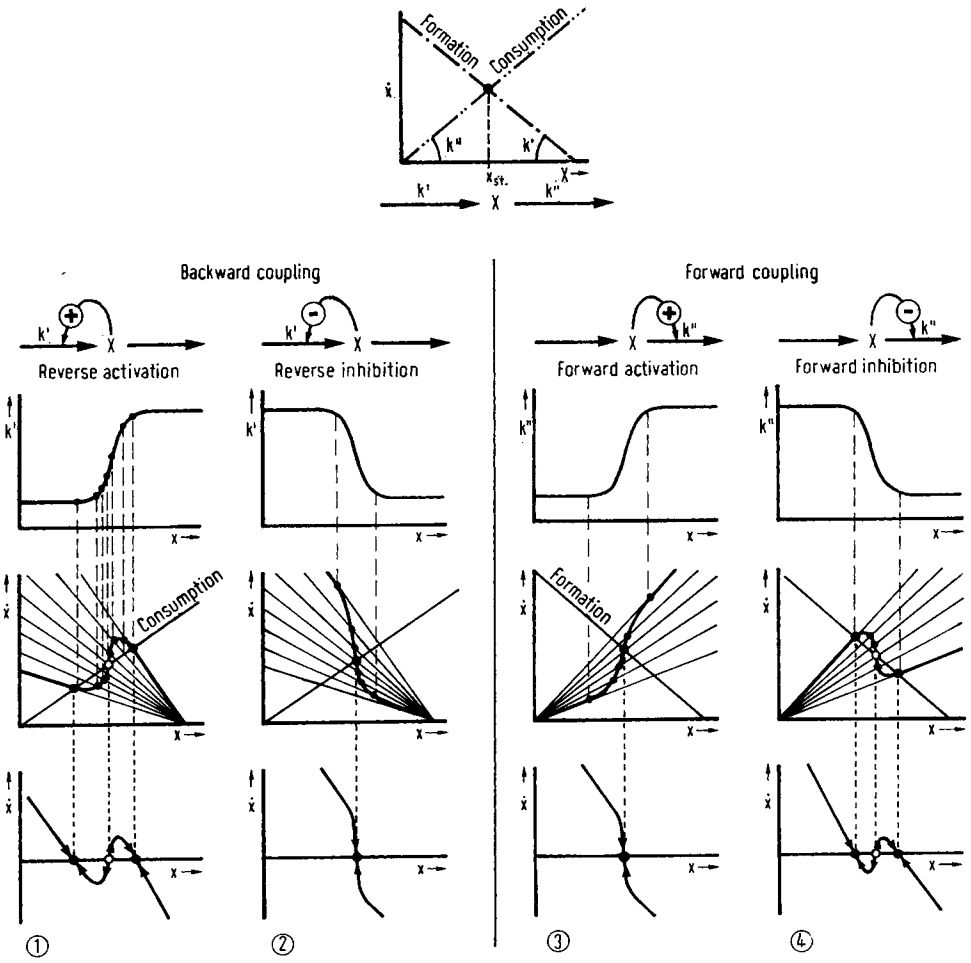


Fig. 18. Occurrence of typical kinetic characteristics by positive and negative feedback. Reverse activation (1) and forward inhibition (4) correspond to positive feedback effects, and reverse inhibition (2) and forward activation to negative feedback effects. $\dot{X} \equiv dX/dt$.

Assuming for the sake of simplicity that the formation and consumption reaction are of first order, a plot of dX/dt *versus* X for these reactions gives two straight lines which intersect at the steady state. Their slopes correspond to the relevant rate constants. Self-coupling alters the slope of one of the two lines according to the value of X: the formation reaction in the case of backward coupling, and the consumption reaction in the case of forward coupling. It can be seen in Figure 18 that non-monotonic characteristics result from positive feedback and monotonic characteristics from negative feedback. Thus, given sufficiently strong positive feedback, bistability and instability arise. Positive feedback therefore labilizes the system and is the actual cause of the propagation phenomenon occurring on adequate ("superthreshold") stimulation.

In contrast, negative feedback has a stabilizing effect and always generates only one stable steady state. The bottom row of Figure 18 shows the "dynamic" diagrams which describe the overall behavior of the feedback systems with respect to the formation and consumption of component X and which illustrate the stability situation by means of the inserted arrows.

Characteristic temporal behavior patterns result for positive and negative feedback, and can be used for experimental determination of the kind of feedback operating in a particular system (Fig. 19)[78]. In the case of positive feedback the system behaves in the manner of a capacitor. If the corresponding characteristic is non-monotonic then the threshold character of the triggering process is apparent.

In contrast, systems with negative feedback behave like an inductance and exhibit characteristic "overshoot" phenomena (see Fig. 2b).

always observed[78]. The oscillations arise from the antagonistic interaction of a relatively fast acting labilizing positive feedback and a slower acting stabilizing (regenerative) negative feedback. This situation can be represented in a simple feedback action scheme (Fig. 20). Hence the occurrence of oscillations depends not only upon the presence of both kinds of feedback but also upon the correct ratio of the action times.

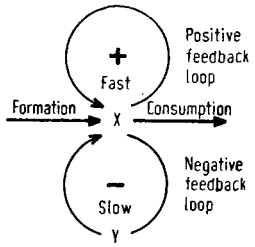


Fig. 20. Principle of antagonistic feedback in oscillatory systems.

As a supplement to Figure 13, the phenomenology of feedback systems and their causes are surveyed in Figure 21.

Each feedback loop can contain several variables in consecutive reactions. All these variables participate in the oscillatory process. In most cases it is possible to decide experimentally to which class of feedback a recorded oscillating variable belongs[78]. As shown by the examples in Figure 22, variables of the positive feedback loop are generally recognizable by pronounced discontinuities or resting points in their oscillograms which are due to the unstable states through which

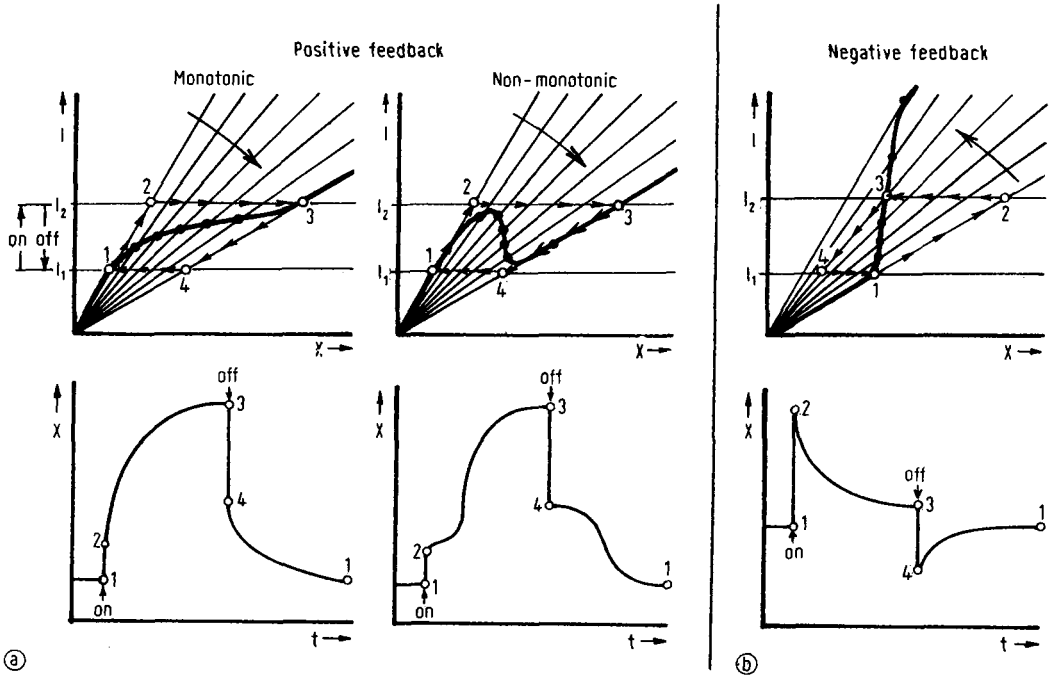


Fig. 19. Temporal behavior of electrochemical feedback systems [78] on sudden change of current. Systems with positive feedback have "pseudo-capacitive" properties, and systems with negative feedback "pseudo-inductive" properties.

On studying chemical oscillations with regard to their temporal behavior, characteristics of both kinds of feedback are

the systems pass. Variables of the negative feedback loop never exhibit such features owing to the absence of instabilities;

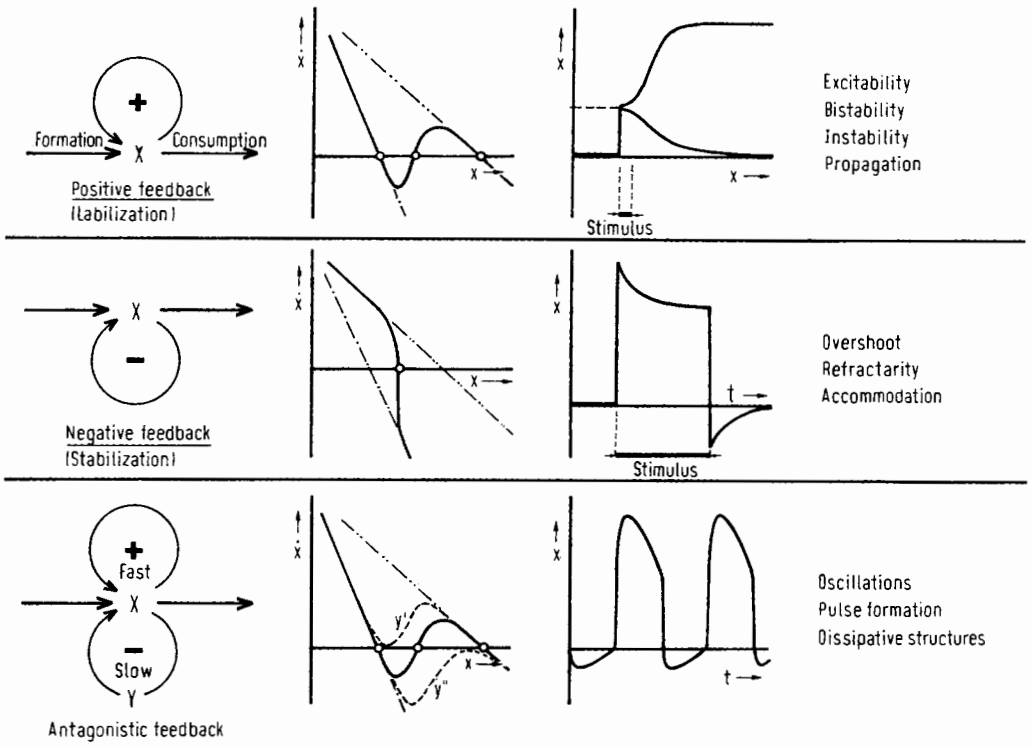


Fig. 21. Phenomenology of coupled systems and assignment to the various kinds of feedback.

their oscillograms therefore usually have a relatively simple sawtooth shape.

Chemical and electrochemical oscillations occasionally occur in chemical engineering, *e.g.* in heterogeneously catalyzed oscillations (Section 2.2.3). However, they have little engineering significance as far as improvement of overall processes is concerned. Instead, they represent an undesirable complication.

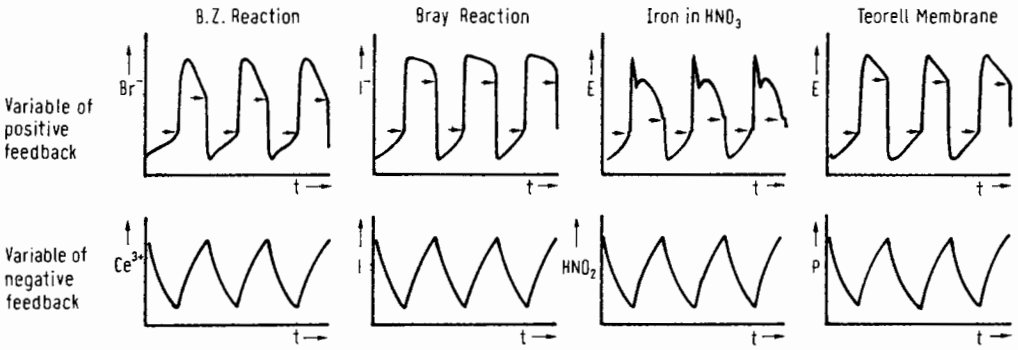


Fig. 22. Simultaneous oscillograms of variables of oscillatory systems [78]. Variables belonging to positive feedback loops generally exhibit flip-flop type oscillograms with characteristic instability features (→). Oscillograms of variables of negative feedback usually have a simple sawtooth shape without instability features (cf. Figs. 1d and 1e). B.-Z. reaction = Belousov-Zhabortinskii reaction.

4. Conclusion

At the close of an article about chemical oscillations it is logical to ask what significance such reactions possess in the various disciplines of science, and especially in chemistry. Are they merely a fortuitous kinetic curiosity whose occurrence is of more academic than practical interest, or are they of fundamental importance in certain scientific, biological, or technical processes.

In the theory of the thermodynamics of non-linear non-equilibrium processes oscillatory reaction courses are particularly striking and interesting phenomena which can only be treated by this theory, still very much in its infancy. It is mainly here that theoretical physics[95] is concerned with chemical oscillations.

Electropolishing processes exist which involve oscillatory activity of the electrode materials to be polished, *e.g.* in the electropolishing of steel in oxalic acid/hydrogen peroxide[96]. However, these are only exceptions in which oscillation kinetics is of engineering utility.

The significance of chemical oscillations in biology presents a completely different picture. The rhythmic nature of processes in bionics, *i.e.* "the chemical engineering of living organisms", has considerable advantages over non-periodic processes. Thus the oscillatory course of enzymatic reactions on a boundary cycle around an unstable steady state leads

to stabilization of the overall process, resulting in enhanced dynamic adaptability to changing external conditions and the possibility of synchronization with simultaneous processes. A rhythmic reaction course is of particular advantage if it leads *via* reaction steps which are mutually exclusive for kinetic reasons.

The orientation of living organisms according to time, *i.e.* the explicit recognition of temporal variables detectable even in single cell organisms such as *Euglena*, *Acetabularia*[97], can be accomplished only by rhythmic processes. In other words, "the biological clock" most probably has to be viewed as an oscillatory chemical mechanism. In the field of enzymatic processes such mechanisms are readily feasible owing to the manifold possibilities of systemic coupling in the metabolism of the living cell.

The ability of the excitable membranes of the nervous system to undergo oscillations permit, as already mentioned, propagation and processing of information.

In the evolutionary process chemical periodicity is also assumed[98] to be operative in spatial differentiation—the formation of defined structures. The activity of such structure-forming oscillatory mechanisms can be directly observed under the microscope, *e.g.* in cell division and in the regeneration of damaged cells.

The elucidation of the diverse manifestations and effects of chemical periodicity, which is clearly essential in living organisms, will only become possible once the kinetics of chemical oscillations can be understood in their elementary form. And this is probably the true reason for the avid interest recently shown in this area.

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Industrial Applications of Photochemical Syntheses

By Martin Fischer[*]

The principal industrial applications of photochemistry have so far been in the fields of free-radical chlorination, sulfochlorination, sulfoxidation, and nitrosation. In addition, however, photochemical reactions are being utilized on an increasing scale for the synthesis of vitamins, drugs, and fragrances. The present article surveys the various kinds of light-induced reactions exploited industrially, the equipment developed, and uses of the photochemical products. Furthermore, the problems encountered in designing a photochemical production plant are discussed for the example of photonitrosation of cyclohexane.

1. Introduction

Most practical applications of photochemistry nowadays lie in areas in which the effect of a photochemical primary process is amplified by a large number of thermal consecutive reactions[1]. This is particularly true of photography, but also applies to photopolymerizations and radical chain syntheses. Use is made of advantageous features of photochemical reaction steps, precise energetic and spatial dosage of light, the high selectivity of individual light reactions, and independence of temperature, consumption of large amounts of light energy being avoided.

So far, there are only few examples of industrial photochemical syntheses with stoichiometric light requirements[2]. The ice was broken by the photonitrosation of cyclohexane (cf. Sections 2.4 and 7).

2. Free-Radical Reactions

The most important applications of photochemical syntheses still lie in the area of radical chain reactions. The 1940's saw the first industrial scale photochlorinations[3]. Since the light output of the mercury vapor lamps then available was but a few hundred watts, the use of light for industrial syntheses apart from vitamin D production was initially restricted to reactions with high quantum yields, *i.e.* to radical chain reactions.

Photochemical initiation of radical chains generally permits relatively low working temperatures, an essential condition for numerous syntheses involving free radicals. Compared with radical chain initiation by thermal decomposition of initiators such as peroxides and azo compounds, light-induced radical generation is of particular advantage in cases where the radical chains are very short and very many initiating radicals are accordingly required.

In the following survey of photochemical chlorination, sulfochlorination, sulfoxidation, and nitrosation the main emphasis is placed on the description of representative industrial equipment[4] rather than the extremely facile chemistry involved. Some details concerning the use of the photochemical products will also be presented.

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2.1. Chlorination

Two different geometrical arrangements of light source and reaction space are employed in industrial photochlorination:

1) The lamp, which is generally shaped as a long cylinder, is fitted with a cooling jacket and immersed in the reaction solution.

2) The reaction solution is contained in a quartz or glass tube which is irradiated externally with one or more lamps.

The immersion well apparatus has the advantage that no light is lost to the surroundings. However, as a drawback, the light intensity falls off very rapidly with increasing distance from the lamp due to absorption by the reactants and to divergence of the light rays (Fig. 1).



Fig. 1. Light intensity distribution in an annular reaction space; L, cylindrical lamp; R, reaction space. Diminution of intensity from the inside to the outside because of a) divergence and b) absorption.

The inhomogeneous distribution of light and the consequent spatial variations in the generation of initiating radicals raises the danger of local overheating because most chlorinations are highly exothermic. Attempts are made to counteract this by thorough mixing of the reaction mixture.

If an empty cylindrical tube is irradiated by a radially symmetric external arrangement of light sources then the radiation density increases towards the axis of the tube owing to convergence of the light rays (Fig. 2a). If the tube is filled with absorbing compounds such as a chlorination mixture, how-

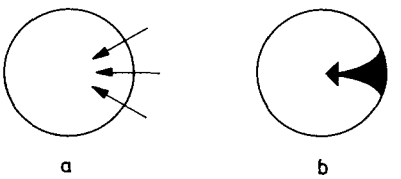


Fig. 2. Light intensity distribution in a cylindrical reaction space radially irradiated from an external source. a) Convergence of the light rays and b) absorption have opposing effects on the light intensity.

ever, the light intensity decreases from the outside to the inside owing to absorption (Fig. 2b).

In this case convergence of the light rays and absorption act in opposite directions and can partly balance each other; on suitable choice of tube diameter and absorption characteristics of the reaction medium a relatively uniform light distribution can be achieved. (For calculations of photoreactions in various irradiation apparatus, see [5].)

Light losses on external irradiation can be minimized by arranging the lamp and reactor tube along the focal lines of an elliptical reflector; an internal cooling tube can be fitted to remove excess heat from the reactor tube (Fig. 3)[6].

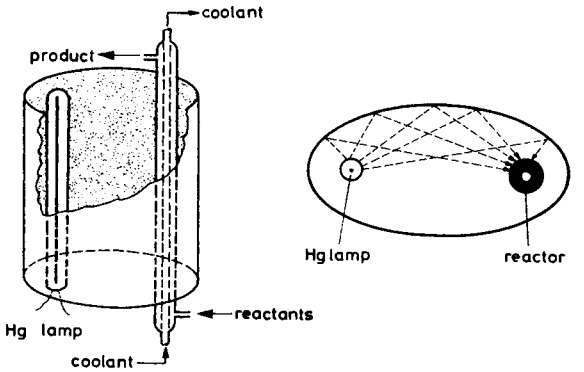


Fig. 3. External irradiation of a tube reactor; the lamp and reactor tube are located in the focal lines of an elliptic reflector. A cooling tube is located in the center of the reactor tube.

In practice, radical chain reactions with high quantum yields are frequently conducted without any great attempt being made to optimize utilization of the light. An example of industrial chlorination in externally irradiated glass tubes was described several years ago by scientists working at Phillips Petroleum[7], *viz.* the production of monochloroalkanes from a C_{11-14} *n*-paraffin cut.

$$RH + Cl_2 \xrightarrow{h\nu} RCl + HCl$$

RH = mixture of *n*-alkanes

The production apparatus essentially consists of two pairs of Vycor tubes (7.5 × 150 cm) and a water-cooled 7.5 kW mercury lamp. A cylindrical reflecting shield of polished aluminum reduces dissipation of light to the surroundings.

Removal of the considerable heat of reaction creates problems in photochlorination in externally irradiated glass tubes. To ensure that the temperature does not rise above 40 °C—uncontrolled decomposition has been observed at higher temperatures—only 15 mol% of chlorine is introduced. Prior to entering the second pair of reactor tubes the reaction mixture is first cooled to *ca.* 5 °C.

Further chlorination to form the undesired dichloro compounds is avoided by stopping the reaction at an overall conversion of 30 %. Owing to the high rate of photochlorination—the residence time of the solution in the irradiated

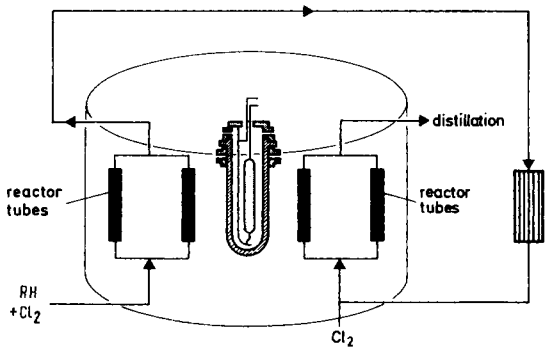
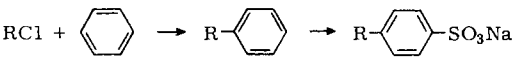


Fig. 4. Industrial photochlorination unit for the production of monochloroalkanes. Two pairs of Vycor tubes are irradiated with a 7.5 kW mercury lamp. RH = mixture of *n*-alkanes.

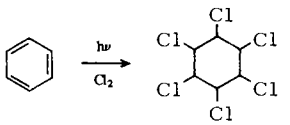
section is only about 20 s—a relatively small production unit of the kind shown in Figure 4 has a production capacity of some 27 t of chloroparaffin per day, corresponding to about 10000 t/a.

Compared to the thermal process, however, the photochemical monochlorination of paraffins is only of minor significance[8, 9].

The chloroalkanes are used for alkylation of benzene to give alkylbenzenes, which serve as starting materials for alkylbenzenesulfonates, an important class of detergents[9].



A chlorination apparatus in which the lamps are surrounded by the reaction solution, *i.e.* in which an annular reaction space is irradiated from its center, has been developed by Ethyl Corporation for the photochlorination of benzene to produce hexachlorocyclohexane[10].



The reactor shown schematically in Figure 5 comprises 18 tube segments, of which 17 are represented by lines. Two 40 W fluorescent lamps are located at the center of each segment. The pump at bottom right rapidly recycles the bulk of the reaction solution in the first 13 segments so that the heat of reaction is efficiently removed by the cooling jacket. A side stream passes through segments 14 to 18 (where residual chlorine reacts) at the same rate as fresh benzene and chlorine are fed in at bottom left.

Plugging of the tubes by crystalline product is avoided by maintaining the concentration of hexachlorocyclohexane in the reaction solution below 15 %. This means that only 4 % of the benzene feed can be converted on passage through the reactor. The chlorine consumption[10] of 270 kg/h in the unit indicates that nearly 3 m^3 of benzene feed is required per hour. The quantum yield of this industrial chlorination amounts to *ca.* 2500.

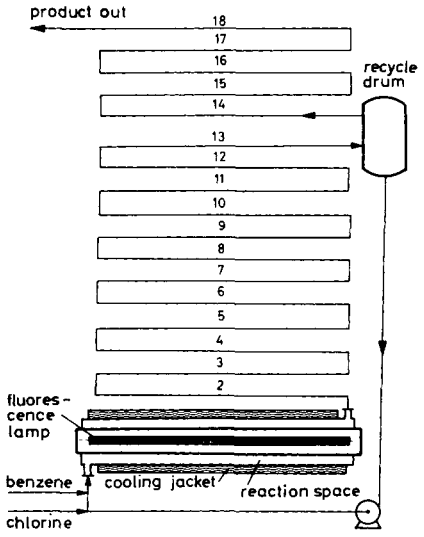
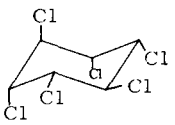


Fig. 5. Reactor for photochlorination of benzene to form hexachlorocyclohexane.

The photoaddition of chlorine to benzene serves for production of the γ-isomer of hexachlorocyclohexane, a versatile insecticide marketed as Lindane or Gammexane (γ-BHC). Unlike other chlorinated hydrocarbons, this plant protection agent still commands considerable interest because it is degraded biologically with comparative ease. The very modest yield of *ca.* 15 % is unsatisfactory, however.



The photochlorination of toluene to benzyl chloride, benzylidene dichloride, and benzotrichloride[11], known to every chemist from his practical course work, should not go without mention. Mixtures of the first two compounds are produced in a series of four lead-lined photoreactors at 80—110 °C[12].

$$C_6H_5CH_3 \xrightarrow[Cl_2]{h\nu} C_6H_5CH_2Cl \xrightarrow[Cl_2]{h\nu} C_6H_5CHCl_2 \xrightarrow[Cl_2]{h\nu} C_6H_5CCl_3$$

Benzyl chloride, also obtained by purely thermal chlorination of toluene, is converted mainly into benzyl alcohol, a well-known fragrance. It is also used in the synthesis of drugs, disinfectants, and emulsifiers[12]. On hydrolysis, or preferably on reaction with benzoic acid, benzylidene dichloride affords benzaldehyde; in the latter case a further valuable intermediate, benzoyl chloride, is also obtained.

$$C_6H_5CHCl_2 + C_6H_5CO_2H \rightarrow C_6H_5CHO + C_6H_5COCl + HCl$$

Benzotrichloride is a valuable intermediate for dyes of the triphenylmethane, xanthene, and anthraquinone series and for plant protection agents.

2.2. Sulfochlorination

Another well known reaction, photochemical sulfochlorination of paraffins, is of great industrial importance[9, 13]. In sulfochlorination the action of light is again limited to the formation of chlorine atoms from chlorine. The sulfonyl chloride group is distributed almost randomly over all C atoms of the hydrocarbon chain[14].

$$RH + SO_2 + Cl_2 \xrightarrow{h\nu} RSO_2Cl + HCl$$

RH = mixture of *n*-alkanes

Clean photochemical sulfochlorination requires the use of unbranched alkanes. Side chains favor competing chlorination. Normal alkanes of high purity are nowadays available in industrial quantities by means of molecular sieve processes.

Sulfochlorination does not stop at the stage of the monosulfonyl chlorides. Since di- and polysulfonyl chlorides have undesirable technical properties the reaction must be stopped at conversions of 30 to 50 %. Yields of 80 to 90 % are then obtained.

Under industrial conditions the quantum yield is about 2000. This means an energy consumption of *ca.* 30 Wh for 1 kg of sulfonyl chloride on use of fluorescent lamps.

Industrial sulfochlorination has been reviewed by *Lindner*[15].

Most of the alkanesulfonyl chlorides produced industrially are hydrolyzed by caustic soda to give water-soluble alkanesulfonates which are used mainly as emulsifiers for polymerizations[9].

$$RSO_2Cl + 2\,NaOH \rightarrow RSO_3Na + NaCl + H_2O$$

Owing to contamination with di- and polysulfonates, which cannot be removed under industrial conditions, the stringent demands nowadays placed on detergents can no longer be fulfilled by this type of alkanesulfonates and they are now hardly used in detergent manufacture[16, 17].

Reaction of alkanesulfonyl chlorides with ammonia leads to sulfonamides, which are used as textile auxiliaries[16] and also reacted further with chloroacetic acid to form a mixture of sulfonylaminoacetic acids. Compounds of this type serve as emulsifiers and as anticorrosion agents for mineral oils[16, 18].

$$RSO_2Cl \xrightarrow{NH_3} RSO_2NH_2 \xrightarrow[NaOH]{ClCH_2CO_2H} RSO_2NHCH_2CO_2H$$

2.3. Sulfoxidation

All the chlorine used in sulfochlorination is eventually recovered as hydrogen chloride or sodium chloride. A far more elegant synthesis of alkanesulfonates has been found in sulfoxidation, in which oxygen serves as oxidizing agent instead of chlorine.

$$RH + SO_2 + {}^1/_2O_2 \xrightarrow{h\nu} RSO_3H$$

$$RSO_3H + NaOH \rightarrow RSO_3Na + H_2O$$

$RH = C_{14-18}$-*n*-alkanes

Photochemical sulfoxidation has been developed as an industrial process at Hoechst[9, 19, 20]. The best one of several variants seems to be the so-called light-water process. The primary sulfoxidation product, peroxysulfonic acid, is trapped by water before it can undergo radical decomposition.

$$RSO_2OOH + H_2O + SO_2 \rightarrow RSO_3H + H_2SO_4$$

An equimolar amount of sulfuric acid is formed as coproduct and has to be removed on work-up.

Figure 6 shows a flowsheet of the industrial sulfoxidation process[20]. The photoreaction occurs in an immersed lamp reactor. A mercury lamp serves as light source. The photoreactor containing paraffin is gassed from below with sulfur dioxide and oxygen (molar ratio 2:1). Thorough mixing is accomplished by circulating the gaseous reactants by means of an external pump. Water is fed in together with paraffin at the top of the reactor. Sulfonic acid and sulfuric acid are continuously extracted into the water, thus largely precluding further reaction of the mono- to di- and polysulfonic acids.

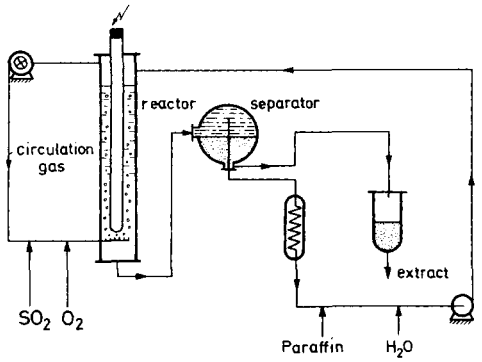


Fig. 6. Simplified flowsheet of the light-water process for sulfoxidation.

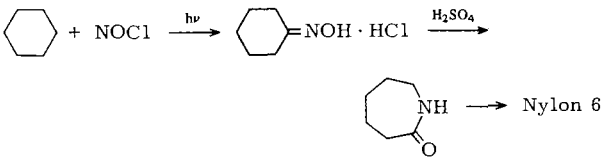
The mixture of aqueous acids is continuously removed in a separator and the unreacted paraffin returned to the photoreactor (Fig. 6). The rather involved isolation of the sulfonic acid[21] will not be considered here.

Compared to conventional photochlorinations or sulfochlorinations the light consumption of sulfoxidation is very high. About 0.2 kWh of electrical energy is required for lamp operation in the production of 1 kg of alkanesulfonate[20]. This means that only *ca.* 1600 t/a can be produced with one 40 kW mercury lamp.

Hoechst presently operates production plants having a total capacity of *ca.* 50000 t/a in the Federal Republic of Germany and France[22].

2.4. Photonitrosation

The light energy costs do not usually play a decisive role in industrial radical chain reactions because the light quanta supplied act with a high multiplication factor. In contrast, photochemical syntheses with quantum yields of about one could only be implemented on an industrial scale once powerful and efficient mercury lamps became available. The development of industrially utilizable lamps was prompted by the photonitrosation of cyclohexane, *i. e.* the light induced reaction of nitrosyl chloride with cyclohexane to form cyclohexanone oxime.



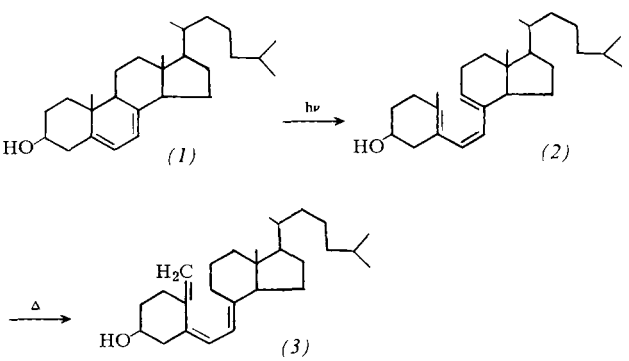
In the 1950's, with the common aim of developing a more economic synthesis of caprolactam, the monomer of nylon 6, several industrial companies and university departments in France, Germany, Japan, the USSR, and the USA started studies on the industrial feasibility of the photonitrosation of cyclohexane. The Japanese chemical company Toray finally decided to conduct the photochemical synthesis in a large production plant[23]. Details are given in Section 7.

3. Photochemical Synthesis of Vitamin D and Related Compounds

3.1. Vitamin D_3

In all the syntheses so far described, radicals, mainly chlorine atoms, are generated in the primary photochemical process. One of the oldest non-radical industrial photoreactions is the synthesis of vitamin D. Whereas vitamin D_2, produced from ergosterol, formerly took pride of place, interest is nowadays focused mainly on vitamin D_3: the latter compound, unlike the former, is also active in poultry. Most of the vitamin D_3 now produced is not used to prevent or cure rickets in children but instead as an additive in animal nutrition.

The starting material for the photochemical synthesis of vitamin D_3 is 7-dehydrocholesterol *(1)*, accessible in four steps from cholesterol[24]. Photochemical ring opening leads initially to previtamin D_3 *(2)*. On heating to 50—80 °C a hydrogen shift occurs to give the thermodynamically more stable vitamin D_3 *(3)*.



Because of the high absorbance of 7-dehydrocholesterol (Fig. 7) photolysis must be performed in relatively dilute solution (*ca.* 1 %). Ethanol or ether serves as solvent[24, 25].

The absorption spectrum of *(2)* completely overlaps that of *(1)*; thus a steadily increasing proportion of the incident

light is absorbed by *(2)* as conversion increases. Unfortunately, the quantum yield of the consecutive photoreaction of *(2)*

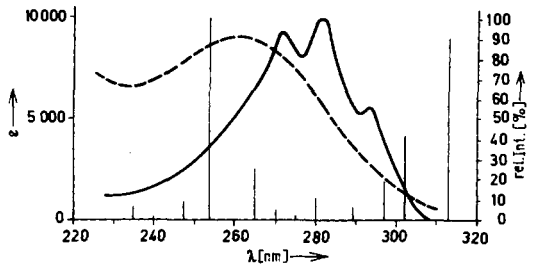


Fig. 7. UV spectra of 7-dehydrocholesterol *(1)* (——) and previtamin D_3 *(2)* (------). Emission lines of the medium pressure mercury lamp.

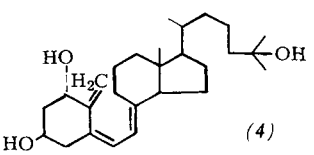
to give tachysterol, the *trans* isomeric triene, is greater than that of its formation[26]. It is therefore essential to stop irradiation of *(1)* once 30—50 % conversion has been reached and to isolate previtamin *(2)*.

The emission of a mercury lamp is regrettably very poorly adapted to the spectrum of 7-dehydrocholesterol *(1)* (Fig. 7): only the relatively weak emission lines at 280, 289, and 297 nm can be exploited, which together amount to only 8.5 mol quanta/h for a 40 kW lamp (total emission over all wavelengths: 174 mol quanta/h)[*].

Given a quantum yield of 0.31 for transformation of *(1)* into *(2)*[26], then $8.5 \times 0.31 = 2.64$ mol of *(2)*/h should be obtainable with a 40 kW lamp. This means that the synthesis of 1 kg of vitamin D_3 requires an irradiation time of 1 h, and thus an energy consumption of 40 kWh. The actual energy required is twice as high: *ca.* 80 kWh/kg vitamin D_3.

3.2. Hydroxy Derivatives of Vitamin D_3

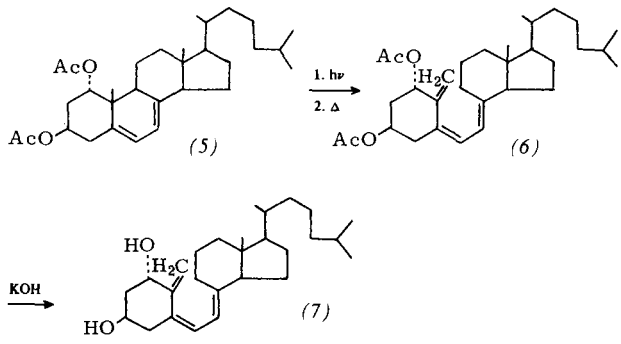
Some years ago it was established[27] that not vitamin D_3 itself but a metabolite formed in liver and kidney, 1α,25-dihydroxyvitamin D_3 *(4)*, is the actual active form responsible for regulating calcium metabolism. Compound *(3)* exhibits very high vitamin D_3 activity in patients having impaired kidney function.



(4)

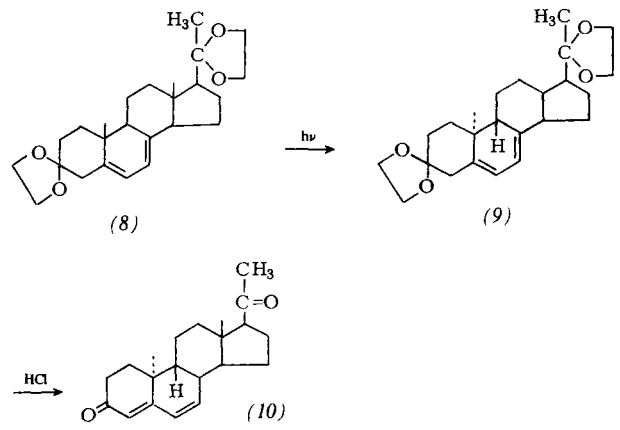
1α-Hydroxy-vitamin D_3 *(7)* proves just as active as *(4)*, but is much easier to produce. The intermediate *(5)* is accessible from cholesterol in six steps[28,29].

The same reaction conditions as established for the parent compound are employed for photochemical ring opening of *(5)* to the previtamin D_3 derivative and subsequent thermal hydrogen shift to give the diacetate *(6)*[28,29]. Alkaline hydrolysis ultimately yields 1α-hydroxy-vitamin D_3 *(7)*. A hydroxylated vitamin D_3 will probably be marketed before long[30].



3.3. Dydrogesterone

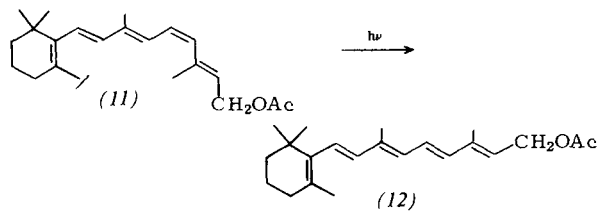
The synthesis of the sexual hormone dydrogesterone *(10)* developed by Philips-Duphar can be regarded as "spin-off" from intensive research work in the vitamin D area[31]. In analogy to the known photochemical transformation of 7-dehydrocholesterol *(1)* into the 10α-methyl isomer lumisterol$_3$, irradiation of the pregnadiene derivative *(8)* gives the retrosteroid *(9)* which is cleaved to form *(10)* by HCl in alcohol.



4. Photoisomerization of Vitamin A Acetate

The Wittig synthesis of vitamin A acetate, performed on an industrial scale at BASF[32], affords a mixture of two stereoisomers, the all-*trans* *(12)* and the 11-*cis* form *(11)*. Only the all-*trans* isomer *(12)* is suitable for use in pharmaceuticals and animal feeds.

A very mild photochemical method has therefore been developed at BASF[33] for converting 11-*cis*- into all-*trans*-vitamin A acetate: it consists in irradiating the stereoisomeric mixture



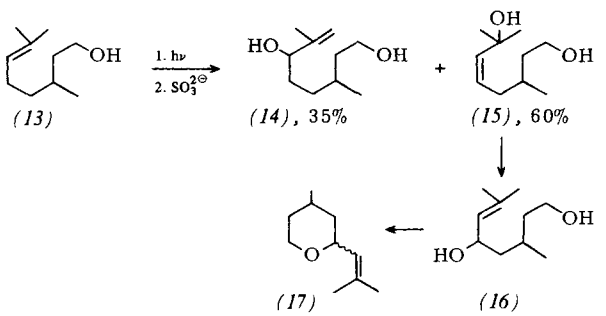
[*] A mol quantum is equal to 6.023×10^{23} photons.

with visible light in the presence of a colored sensitizer such as tetraphenylporphinatozinc or chlorophyll. A photochemical isomerization process which can also be used for transforming the 9-*cis* isomer into the all-*trans* form was recently described in a patent application by Hoffmann-La Roche[34].

5. Photooxygenation

5.1. Rose Oxide

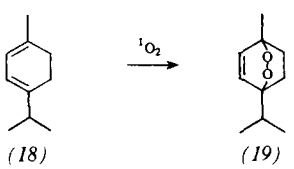
A further highly promising field for industrial photochemistry is the synthesis of fragrances. Small scale production of rose oxide *(17)* is already being conducted at the Firmenich and Dragoco companies.



Photooxygenation of citronellol *(13)* with rose bengal as sensitizer gives a mixture of two isomeric hydroperoxides[35] which can be reduced by sulfite to the alcohols *(14)* and *(15)*. The main product *(15)* undergoes allylic rearrangement to *(16)* in acid solution; *(16)* cyclizes with elimination of water to rose oxide *(17)*.

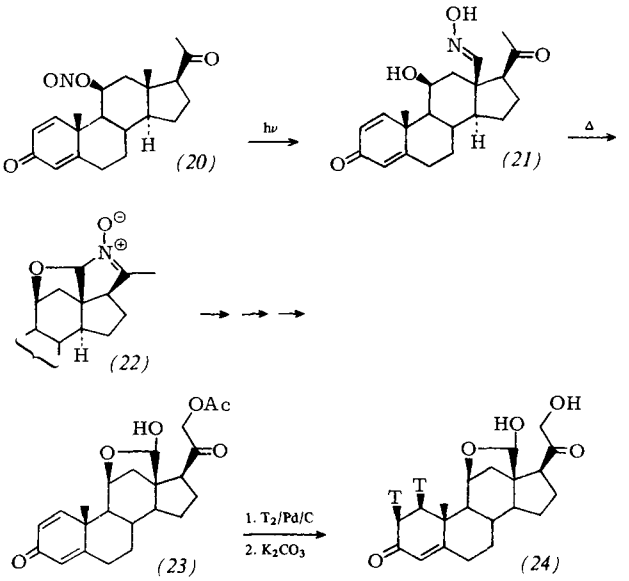
5.2. Ascaridole

Another sensitized photooxidation, *i.e.* reaction of α-terpinene *(18)* with singlet oxygen to give ascaridole *(19)*, acquired some importance after World War II[36]. It is no longer performed owing to the toxicity of this anthelmintic.



6. The Barton Reaction

The functionalization of saturated carbon atoms by photolysis of nitrites, discovered by *D. H. R. Barton*[37], is used in the production of tritium-labeled aldosterone *(24)*. The photochemical step of the multi-step synthesis consists in the transformation of the pregnane derivative *(20)* into the C-18-oxime *(21)* which gives the nitrone *(22)* on heating[38].



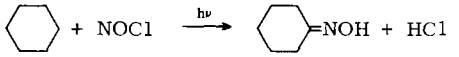
Compound *(22)* can be converted in a series of conventional steps into 1,2-didehydroaldosterone acetate *(23)* which yields the radioactively labeled aldosterone *(24)* by catalytic tritiation and subsequent hydrolysis[39]. The American company New England Nuclear produces *(24)* on a small scale for use as a medical diagnostic aid.

7. Scale-up of Laboratory Photoreactions to Industrial Processes: Photonitrosation of Cyclohexane

Further development of the technology of photochemical processes is of crucial significance for the future of industrial photochemistry. The present state of the art can best be described with the aid of an example, the photonitrosation of cyclohexane already mentioned above.

7.1. The Problem

In the interest of a readily comprehensible presentation of technical aspects, let us consider the decision processes that an industrial chemist faces and the data he works with when scaling-up a photochemical reaction from the laboratory



to a production plant for the case of the photochemical synthesis of cyclohexanone oxime. Assuming that a photochemical plant for producing 10000 t/a of cyclohexanone oxime were to be developed: What typically photochemical questions arise? What parameters play an essential role on scale-up? And finally: What kind of photoreactor design is particularly suitable for large-scale manufacture of oxime?

7.2. Laboratory Results as the Basis of Planning

The starting point for the design of an industrial plant is the results of laboratory experiments on photonitrosation.

The various process steps are simulated on a small scale under conditions corresponding as closely as possible to those met in practice to permit early detection and mastering of fundamental technical problems.

Photochemical synthesis of cyclohexanone oxime can be performed in the usual immersion well apparatus fitted with a medium pressure mercury vapor lamp (Fig. 8)[41].

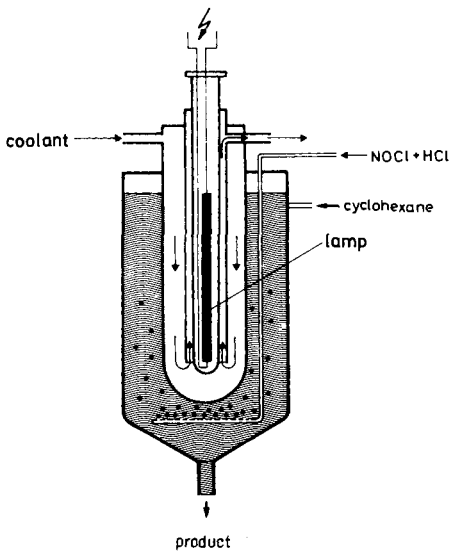
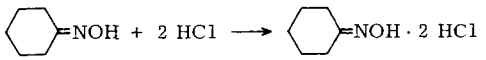


Fig. 8. Immersion well apparatus for photonitrosation on a laboratory scale. The mercury lamp is located at the center of a cold finger, NOCl and HCl are blown in through a glass frit. The oily bis(hydrochloride) of the oxime can be withdrawn from the bottom.

With a view to the design of large-scale industrial plant, continuous operation should already be aimed at in the laboratory. Cyclohexanone oxime can readily be removed from the irradiation apparatus as the bis(hydrochloride) which has a greater specific gravity and is insoluble in cyclohexane if hydrogen chloride is fed into the reactor together with nitrosyl chloride[40].



Continuous long-term experiments required for ascertaining optimum reaction conditions and determining the capacity of the laboratory apparatus are precluded by formation of a light-absorbing tarry deposit on the surface of the lamp cooler[23,40,44]. The short-wavelength emission of the mercury lamp is mainly responsible for formation of this coating[44,45]: If the emission between 248 and 366 nm is filtered out by addition of sodium nitrite to the cooling water of the lamp then photonitrosation can be performed for several days without significant coating[46].

Under optimum conditions the yield of oxime is 89 %[41]. The most important by-product is chlorocyclohexane, which has to be removed by distillation to prevent its accumulation.

Owing to the low absorbance of nitrosyl chloride in the long-wave region (Fig. 11) and to the limited layer thickness in laboratory apparatus, the light is not completely absorbed. It is therefore impossible to determine the maximum product output for a lamp of given wattage in the laboratory.

When beginning to design a production plant on the basis of the above laboratory results very many questions have to be answered, for example: Are the starting materials, especially nitrosyl chloride, available in industrial quantities? What materials of construction apart from glass are sufficiently resistant to the exceptionally corrosive reaction mixture? What measures can be adopted to ensure optimum temperature control and mixing in the photoreactor? How is the oxime best isolated? How can the accumulation of by-products be avoided?

These questions, which occur in modified form in the design of very many chemical production plants, are not necessarily typical of a photochemical process. They will therefore be put aside in favor of specifically photochemical problems.

7.3. Choice of Lamp

A very important condition for the design of a photoprocess is a knowledge of commercially available lamps[4]. The most powerful present-day lamps are medium pressure mercury vapor lamps with a power consumption of 60 kW. A schematic diagram of such a lamp fitted with cooling jacket is shown in Figure 9. The lamp is *ca.* 2 m long and 6 cm in diameter, and can be cooled with water or a filter solution.

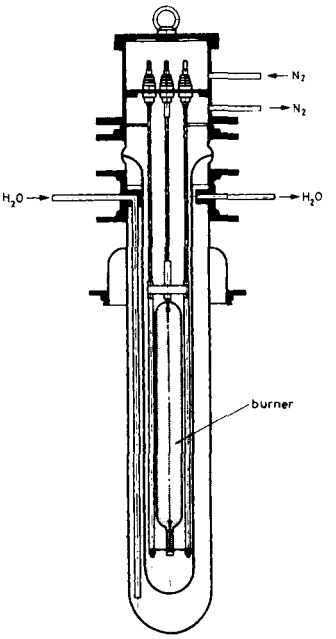


Fig. 9. 60 kW mercury lamp with cooling jacket.

Figure 10 shows a 60 kW lamp shortly after ignition. A 60 kW mercury lamp costing about $ 1500.—[*] without cooling jacket can be run for up to a year without significant loss of output provided that it is not switched off and on too frequently[23].

[*] Mercury lamps for industrial processes are available from Quarzlampen GmbH, Hanau, and Comp. Electromécanique Etabl. SCAM, Paris.

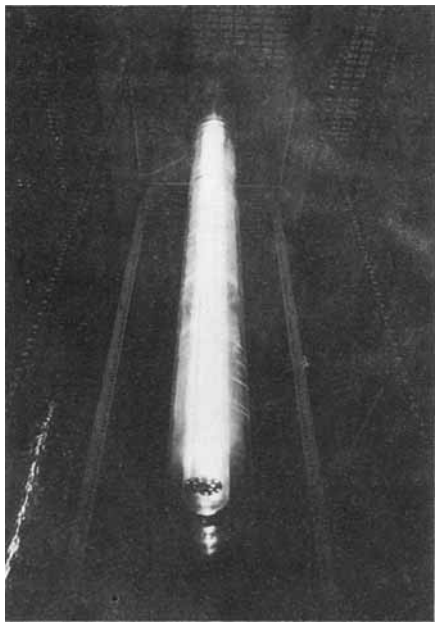


Fig. 10. 60 kW mercury lamp with cooling jacket. The lamp was photographed shortly after being switched on before it was burning brightly.

It is important that all the emission lines of the mercury lamp in the ultraviolet and visible region of the spectrum be absorbed to a greater or lesser extent by nitrosyl chloride in order to ensure a good utilization of the light energy (Fig. 11). Overlap is seen to be considerably better than in the synthesis of vitamin D because of the broad absorption bands of nitrosyl chloride.

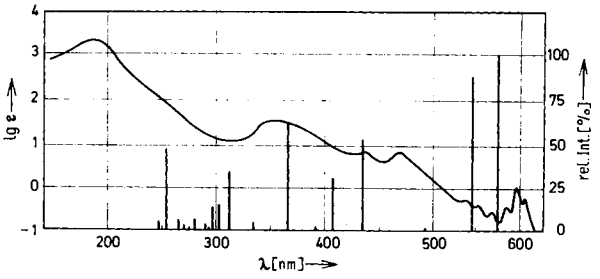


Fig. 11. Absorption spectrum of nitrosyl chloride and emission lines of an undoped mercury lamp. The relative intensity of the emission lines (right-hand scale) refers to mol quanta/h and not to the wattage.

Unfortunately, however, deposit formation on the immersion well precludes use of the emission lines between 248 and 366 nm for photonitrosation. Thus *ca.* 43 % of the overall light emission of the lamp cannot be used. A shift to the desired spectral region of 400—600 nm can be induced by addition of small amounts of thallium iodide to the mercury discharge. This doping causes a very intense emission at 535 nm at the expense of all mercury lines (Fig. 12).

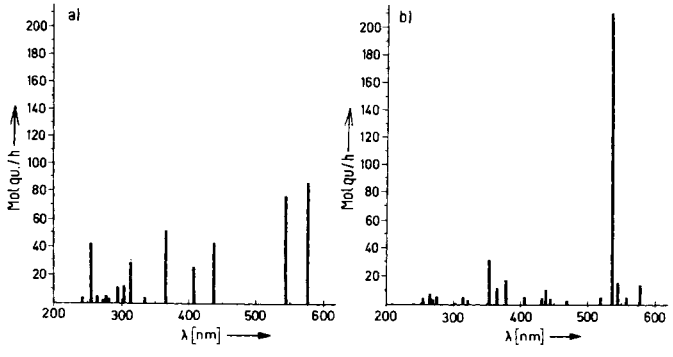


Fig. 12. a) Emission spectrum of an undoped mercury lamp; b) emission spectrum of a mercury lamp doped with TlI.

7.4. Number of Lamps Required

Once the type of lamp required for the production plant—a Tl-doped mercury lamp—has been established[47], it is logical to ask how many lamps will be required for the projected capacity of 10000 t/a of oxime, or how much product can be expected per year from a single 60 kW lamp.

The most reliable method of determining this quantity is undoubtedly to build a pilot reactor with a 60 kW lamp and to test it. However, it is relatively easy to estimate the amount of product expected from the light emission of the doped mercury lamp and the quantum yield of oxime formation. The output of a Tl-doped 60 kW mercury lamp at 535 nm is 13.1 kW or 210 mol quanta/h. Assuming a quantum yield of 0.8 under industrial conditions[42,43], 168 mol or 19 kg of oxime can be expected per hour.

Formation of up to 0.4 kg oxime/kWh power consumption of the lamp was determined by experiment; this corresponds to 24 kg/h for a doped 60 kW lamp. The discrepancy between this figure and the above estimate comes about because the weaker lines (Fig. 12b) also contribute to oxime formation in addition to the emission at 535 nm.

24 kg of oxime per hour corresponds to a capacity of 200 t/a for one 60 kW lamp. Hence it follows that the projected 10000 t/a plant will require 50 lamps.

7.5. Arrangement of Lamps in an Industrial Photoreactor

It would be quite feasible to install 50 photoreactors in parallel. However, in view of the fact that each reactor would have to be fitted with numerous supply lines for starting materials and products, for electrical energy and the filter solution for cooling the lamps, the construction of 50 individual reactors appears a very complicated and expensive task. It is much more reasonable to develop photoreactors containing say 50 lamps instead of just one.

A photoreactor fitted with 50 industrial mercury lamps will have to be designed in a completely different way from the laboratory immersion well apparatus with only one light source. A question of paramount importance in the construction of a multi-lamp reactor will concern the geometrical arrangement of the individual 60 kW lamps, which in turn determines the light distribution.

The mechanical sensitivity of the lamp cooling wells, which are at least 2.5 m long, immediately suggests that the lamps

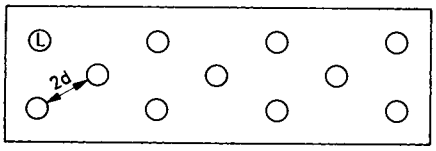


Fig. 13. Arrangement of several lamps L (shown in section) in a rectangular reaction vessel.

should be suspended in the reaction solution from above. What is the optimum distance of the lamps from one another and from the walls of the reactor (Fig. 13)?

Asked in another way: How far does the light emitted from a lamp penetrate the reaction solution before it is largely absorbed?

The thickness of the layer of solution which absorbs 99% of the light of wavelength 535 nm can be approximately calculated with the aid of equations (a) and (b) (see Fig. 14). In

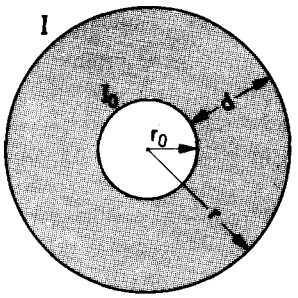


Fig. 14. Layer of liquid reached by the light from a lamp. r_0 = radius of the lamp cooling jacket; d = thickness of layer of solution absorbing 99% of the light; I, I_0 = intensity of light.

a first approximation the light is assumed to be emitted radially and light scattering by the heterogeneous reaction mixture is considered insignificant.

$$\log\frac{I_0}{I} = \log\frac{r}{r_0} + 2.3\cdot\varepsilon_c(r-r_0) \qquad \text{(a)}$$

$$d = r - r_0 \qquad \text{(b)}$$

If I_0 is the intensity of light at the surface of the lamp cooler, $I = 10^{-2} I_0$ = intensity of light at a distance d from the lamp, $\varepsilon = 0.9$, $c = 0.037$ mol NOCl/l, and $r_0 = 10$ cm, the value of r is calculated as 30 cm, and the thickness d of the layer in which the light is almost completely absorbed is 20 cm.

The distance between two lamps should accordingly not exceed 40 cm if dark zones are to be avoided. Experiments confirmed the suitability of this distance[23].

The region still reached by the light from a given lamp will of course depend upon the wavelength. Light of shorter wavelength such as the intense 366-nm mercury line is absorbed in a much thinner layer of only 0.4 cm, corresponding to the higher absorbance of NOCl at this wavelength.

Thus the oxime due to short wave light is formed in the immediate vicinity of the lamp. It is therefore hardly surprising that the hydrophilic oxime bis(hydrochloride) which is insoluble in cyclohexane is deposited on the likewise hydrophilic glass of the cooling well where it resinifies under the action of light and nitrosyl chloride to form a tarry deposit. As already mentioned, however, formation of this coating can be largely suppressed by use of a filter solution for elimination of UV light.

7.6. Example of an Industrial Multi-lamp Reactor

A rectangular plan appears to be the most suitable for an industrial multi-lamp reactor. The individual lamps could then be arranged as shown in Figure 13. Figure 15 shows a section through a multi-lamp reactor proposed by the Toray company[48].

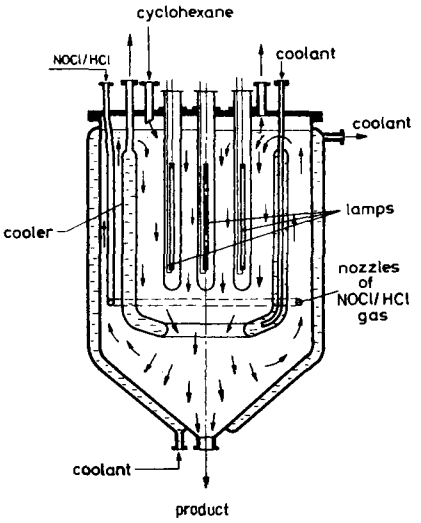


Fig. 15. Section through a photonitrosation reactor (after [48]).

Apart from the lamps, an opaque wall carrying coolant is also incorporated in the tapered trough. The reaction gases NOCl and HCl are introduced into the outer compartment of the reactor. The cyclohexane in this space is carried along by the rising gases and simultaneously saturated with NOCl and HCl. The liquid phase flows in direction indicated by arrows past the lamps, whereupon the oxime bis(hydrochloride) is formed and sinks to the bottom as fine oil droplets. The droplets coalesce during their downward passage to give a high density oily liquid which travels down the inclined floor of the vessel and can be withdrawn from the bottom. The insolubility of the oxime bis(hydrochloride) thus permits facile product removal and hence continuous operation so important for an industrial synthesis.

Figure 16 shows a view of the upper part of the Toray industrial photoreactor. The tops of the lamps housing the electrical supply lines can be recognized.

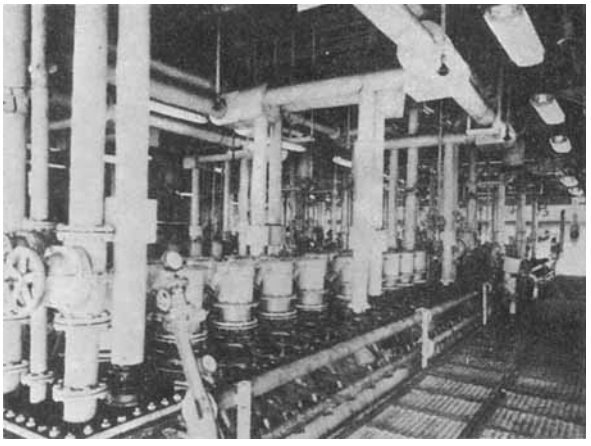


Fig. 16. Photograph of an industrial photoreactor operated by the Toray company [23].

The photochemical aspects emphasized in this account represent but a small part of the enormous task of developing

a plant for the photochemical production of cyclohexanone oxime. The choice of materials of construction was particularly difficult because the reaction mixture is highly corrosive towards all the usual materials. The only material sufficiently resistant for use as reactor lining is the very expensive titanium[44].

Problems of cooling, mixing, replacement of burnt-out lamps, and removal of deposits which cannot be avoided in long-term operation, can only be mentioned in passing.

A vital question for all commercial scale photochemical syntheses is that of safety, arising from the close proximity of the lamp—an 800 °C hot source of ignition—and flammable liquids. In order to control these hazards the lamps are run in a nitrogen atmosphere and an automatic shut down device switches them off automatically in the event of a breakdown, *e.g.* failure of the cooling water supply or a temperature rise in the reactor.

Development of a photochemical process for the synthesis of caprolactam is not restricted to the design of a photoreactor. Economical production processes are also required for nitrosyl chloride and for the Beckmann rearrangement of the oxime to the lactam[23,44]. We shall not consider these processes here.

7.7. Economics of Photonitrosation

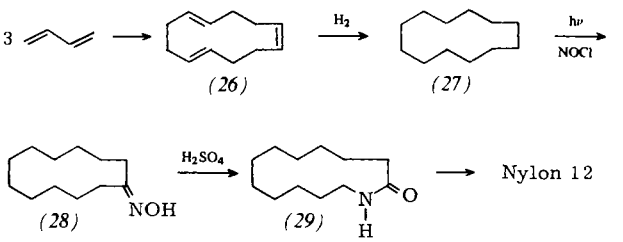
Questions of economics are of supreme importance for the industrial realization of a large-scale photochemical process[49]. For the photochemical synthesis of cyclohexanone this means that the production costs should not be higher than those of conventional processes based on phenol or toluene. The photochemical synthesis has the advantage of fewer steps and higher overall yields than competing processes. However, the fact that only one company has decided to employ the photonitrosation process suggests that the photochemical lactam synthesis does not have any cost advantages over conventional syntheses. Some 160000 t/a of caprolactam are now produced by the photonitrosation process at Toray[49].

In this connection, the cost of energy and lamps incurred by the photochemical synthesis step is very important: it has already been mentioned that the production of 1 kg of cyclohexanone oxime requires 2.5 kWh of electrical energy for operating the lamps. At a price of 5 cents/kWh, the energy costs amount to 12.5 cents/kg of oxime. The cost of the lamps calculated from the capacity, lifetime, and initial purchase price is 1 cent/kg, which is a relatively low value.

These data clearly show that a photochemical synthesis step does not have to be expensive, provided that the quantum yield is not much lower than unity and the photoreactive starting material also absorbs in the long-wavelength region of the spectrum. Long-wavelength light is less expensive than short-wavelength light because the individual quanta contain less energy, and high-performance sources are available for visible light.

8. Lauryllactam by Photonitrosation

Apart from the synthesis of caprolactam, photonitrosation has meanwhile found a second industrial application: the production of lauryllactam, the monomer of nylon 12[50]. In place of cyclohexane, cyclododecane *(27)*, accessible from butadiene *(25)* in two steps, is converted into the oxime *(28)* by nitrosyl chloride and light.



On account of its low density and low absorption of water, lauryllactam *(29)* is used for a number of special purposes, in particular for the production of dimensionally stable plastic components (automobile construction) and for plastic coating of metals[51].

The photochemical lauryllactam process was developed by ATO in France. The photochemical plant having a present capacity of 8000 t/a comprises several photoreactors, each containing 27 lamps of 60 kW power consumption[52].

9. The Importance of Industrial Photochemistry

In his comprehensive monograph "Allgemeine Photochemie" written some 40 years ago, *Plotnikow* predicted that photochemical syntheses on an industrial sclae would be limited to a few special cases, *i.e.* to the production of particularly expensive specialties[53]. He justified this statement by pointing out that light reactions generally require irradiation of large surface areas which would incur very high costs. In *Plotnikow*'s opinion, a tree is an ideal photochemical factory; its leaves present a maximum absorption area for a minimum volume. He urgently warned against any, necessarily imperfect, imitation of Nature.

Nowadays, light reactions have acquired a firm place in the armamentarium of industrial methods. The foundations of photochemical technology have been laid, for it is now possible to scale-up photoreactions from the laboratory to production units employing 40- or 60 kW lamps.

The space-time yields of non-radical photochemical syntheses, which are still frequently unsatisfactory, should be improved by the development of even more powerful lamps; prototypes of 100 kW mercury lamps have already been constructed.

Numerous patent applications indicate that although light will continue to be used predominantly for initiating radical chain reactions, its use in the production of synthetically demanding products for drugs, plant protection, and fragrances will steadily increase. Thus our extensive knowledge about the manifold possibilities of photochemical syntheses[54] will find more and more practical application.

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Organomercury Compounds in Organic Synthesis

By Richard C. Larock[*]

Organomercurials have been known since 1850 and many synthetic routes to these compounds presently exist. The ability of these compounds to accommodate a wide variety of functional groups and to tolerate quite diverse reaction conditions makes them attractive as synthetic intermediates. While the solvomercuration-demercuration and divalent carbon transfer reactions remain the most widely used of the organomercurial reactions, a number of new synthetic procedures employing organomercurials have been developed in recent years. Many of these involve transmetallation reactions with palladium salts.

1. Introduction

Organomercurials were among the first organometallic compounds to have been prepared over 125 years ago. Early interest in their medicinal use encouraged chemists to synthesize many organomercurials. Although these compounds found increasing utility in the synthesis of other organometallic compounds, their low chemical reactivity towards organic substrates limited their early use in organic synthesis. With the development of the more reactive Grignard and organolithium reagents, interest in the synthetic applications of these compounds waned. However, with the increasing interest in recent years in the development of organometallic reagents which will undergo mild carbon-carbon bond formation and yet tolerate a variety of functionality, the organomercurials have seen a rebirth of interest. The ready availability of these compounds, their ability to accommodate essentially all important organic functional groups, and their remarkable chemical and thermal stability have made them attractive as synthetic intermediates. These factors plus the ease with which these compounds undergo transmetallation reactions with a number of transition metals, most notably palladium, have provided a large number of new procedures which should prove of interest to the synthetic organic chemist.

This review will only very briefly outline some of the methods of synthesis of organomercurials which have proven useful in the development of these compounds as reagents and intermediates in organic synthesis. The major portion of the review will then cover a number of new synthetic applications of these compounds. Only those reactions whose generality has been established will be covered. No attempt will be made to cover any of the uses of mercury salts as oxidizing agents in organic chemistry. The use of mercury(II) oxide in this respect has already been extensively reviewed[1].

2. Synthesis of Organomercury Compounds

Today a wide variety of synthetic procedures exist for the preparation of organomercurials. These methods have been reviewed in two recent books[2, 3]. Only those reactions which lead to synthetically valuable organomercury reagents or intermediates will be mentioned here.

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The direct synthesis of organomercurials from organic halides and metallic mercury or mercury amalgams is rather limited [eq. (1)][4]. However, methyl, methylene, benzyl, propargyl and several allylic and β-acylvinyl iodides undergo a facile reaction in the presence of light. Alkyl bromides will react when activated by electron withdrawing groups, but alkyl chlorides are generally unreactive. Utilization of mercury amalgams usually results in formation of the corresponding diorganomercury compounds of type HgR_2, but the yields are generally low.

$$R{-}X + Hg \rightarrow R{-}Hg{-}X \quad (1)$$

Organomercurials are most commonly prepared from the corresponding organolithium or -magnesium compounds [eqs. (2) and (3)][5]. However, the severe limitations on functionality and the already numerous synthetic applications of these highly reactive organometallics severely restrict the synthetic utility of the resulting organomercury compounds.

$$RLi + HgX_2 \rightarrow RHgX + LiX \quad (2)$$

$$RMgX + HgX_2 \rightarrow RHgX + MgX_2 \quad (3)$$

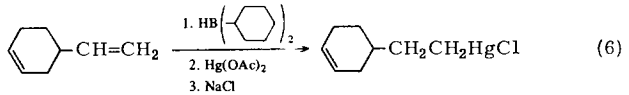
Halomethylmercury compounds have proven very valuable as carbene transfer reagents. They are most readily obtained by carbanion displacement reactions on organomercury halides [eq. (4)][6]. A large number of these reagents have been prepared and many are now commercially available. Their utility as transfer reagents will be discussed in Section 4.

$$RHgX + HCX_3 + KOC(CH_3)_3 \xrightarrow[THF]{} RHgCX_3 + HOC(CH_3)_3 + KX \quad (4)$$

The mercuration of organoboranes offers a very valuable method for the synthesis of organomercurials containing a variety of functional groups[7]. Primary trialkylboranes, readily available *via* hydroboration of terminal olefins, undergo a rapid quantitative reaction with mercury(II) acetate at room temperature to give the corresponding alkylmercury acetates [eq. (5)][8]. Treatment with aqueous sodium chloride provides excellent yields of the alkylmercury chlorides. Secondary alkyl groups do not react under these mild conditions allowing

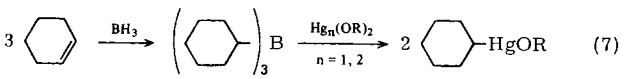
$$3RCH{=}CH_2 \xrightarrow{BH_3} (RCH_2CH_2)_3B \xrightarrow{3Hg(OAc)_2} 3RCH_2CH_2HgOAc \quad (5)$$

the use of dicyclohexylborane for selective hydroboration-mercuration [eq. (6)]. Dialkylmercury compounds can be prepared



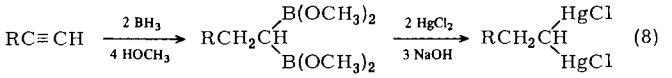
(6)

in a similar manner[9]. Secondary alkylmercury compounds are readily obtained from internal olefins *via* hydroboration-mercuration using mercury alkoxides [eq. (7)][10,11].

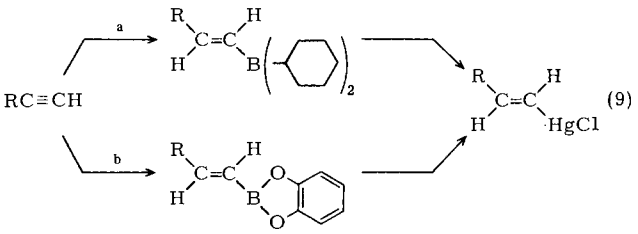


(7)

The hydroboration-mercuration of alkynes can be controlled to give either alkylidenebis(mercury(II) chlorides) [eq. (8)][12] or vinylmercury(II) chlorides [eq. (9)][13,14]. The dicy-



(8)



(9)

clohexylborane route (Route a) to vinylmercurials gives excellent yields from terminal alkynes and has been shown to tolerate functional groups[13]. The "pyrocatecholborane" procedure (Route b) is superior for the conversion of internal alkynes to vinylmercurials[14].

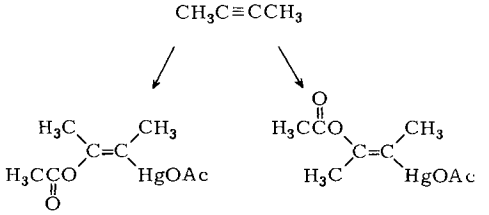
In a protic solvent mercury salts react directly with alkenes to form a wide variety of very valuable β-substituted organomercurials [eq. (10)][15]. These reactions have proven exceed-



(10)

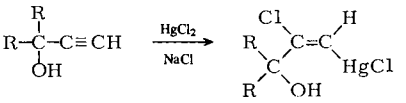
ingly useful for the Markownikoff functionalization of alkenes when employed in conjunction with a demercuration step, and will be discussed in detail in Section 3.

At this time we will discuss only the analogous alkyne addition reactions which lead to organomercurials useful in other synthetic transformations. Mercury(II) acetate readily reacts with internal alkynes in acetic acid to give β-(acetoxy)-vinylmercurials. Depending upon reaction conditions, 2-butyne gives either the *trans* or the *cis* addition product [eq. (11)][16]. Certain propargylic alcohols and diols react readily



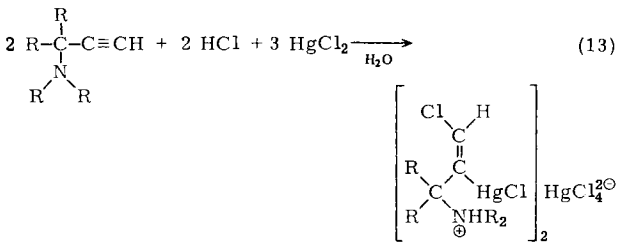
(11)

with saturated aqueous solutions of mercury(II) chloride and sodium chloride to give the corresponding *trans*-β-chlorovinylmercury(II) chlorides [eq. (12)][17]. We have also recently



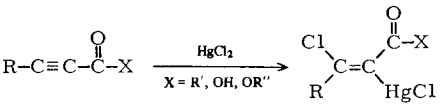
(12)

observed analogous addition reactions with alkynylamines in dilute hydrochloric acid [(eq. (13)][18]. Ketones, carboxylic



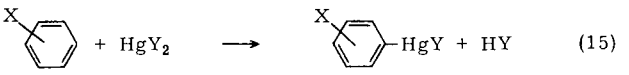
(13)

acids and esters containing a CC triple bond also undergo similar addition reactions [eq. (14)][19,20].



(14)

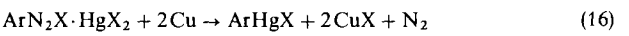
The most important route to arylmercurials is undoubtedly the direct mercuration of aromatic compounds [eq. (15)][21,22].



(15)

This reaction has been extensively studied from both a mechanistic and synthetic standpoint. It generally exhibits the characteristics of a typical electrophilic aromatic substitution reaction and is facilitated by highly ionic mercury salts and by electron donating groups on the aromatic ring. Arylmercurials containing a large variety of organic functional groups have been prepared in this manner.

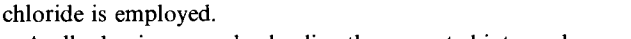
The direct mercuration of aromatic compounds has one major drawback. It often results in mixtures of *o*, *m*, and *p* isomers. This complication can be easily avoided by employing diazonium salts[23]. Copper promotes the facile displacement of nitrogen from the double salts of aryldiazonium halides and mercury(II) halides [eq. (16)]. With excess copper and



(16)

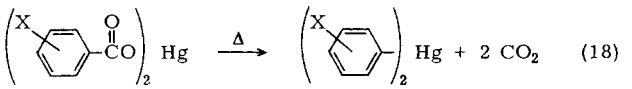
aqueous ammonia diarylmercury compounds are produced. These reactions also proceed in high yield when copper(I) chloride is employed.

Arylhydrazines can also be directly converted into arylmercurials upon treatment with mercury(II) acetate and copper(II) acetate [eq. (17)][24].



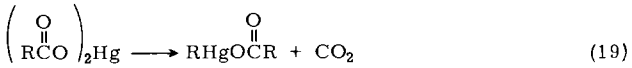
(17)

The thermal decarboxylation of the mercury(II) salts of arenecarboxylates provides an alternate method for the synthesis of arylmercurials, but appears limited to aryl groups containing strong electron withdrawing groups [eq. (18)][25].



(18)

The photochemical or peroxide initiated decomposition of aliphatic or aromatic mercury carboxylates proceeds under much milder conditions and often provides excellent yields of the corresponding organomercury carboxylates [eq. (19)][26].

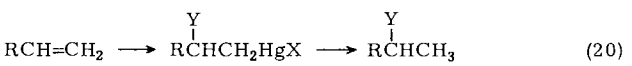


(19)

Although this discussion of the preparation of organomercurials has been kept purposely short, it is obvious that a wide variety of methods for their synthesis exist and that a substantial number of these methods are quite general and accommodate considerable organic functionality. With this in mind we are ready to explore some of the synthetic applications of these compounds.

3. Solvomercuration-Demercuration Reactions

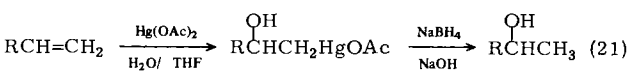
The solvomercuration-demercuration of alkenes is probably the most important synthetic method employing intermediate organomercurials [eq. (20)]. This sequence has provided a



(20)

very general method for the Markownikoff functionalization of alkenes. Its advantages over other procedures are: (1) extremely mild reaction conditions are involved, (2) considerable functionality is accommodated, (3) carbon skeletal rearrangements are rare, and (4) numerous nucleophiles, Y, can be employed. We shall only very briefly cover each of the different types of solvomercuration adducts which can be formed and the major methods by which they can be demercurated. Primary emphasis will be on those procedures which accomplish the above transformation *in situ*, without isolation of the intermediate organomercurial, as these are clearly the synthetically more appealing procedures.

The oxymercuration-demercuration reaction is the most widely used synthetic procedure [eq. (21)]. It provides



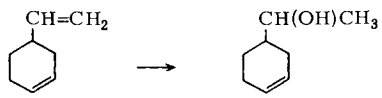
(21)

a very convenient procedure for the Markownikoff hydration of alkenes, nicely complementing hydroboration-oxidation. Although many β-hydroxyalkylmercurials have been isolated from this reaction[27], and a few subsequently reduced with various reducing agents, the recent work of *H. C. Brown et al.* on the *in situ* oxymercuration-demercuration of alkenes using sodium tetrahydridoborate as the reducing agent provides the most convenient procedure[28]. This procedure is applicable to mono-, di-, tri- and tetraalkyl, as well as phenyl substituted alkenes. The relative rates of hydroxymercuration have also been determined[29]:

$$R_2C{=}CH_2 > RCH{=}CH_2 > \textit{cis}\text{-}RCH{=}CHR > \textit{trans}\text{-}RCH{=}CHR > R_2C{=}CHR > R_2C{=}CR_2$$

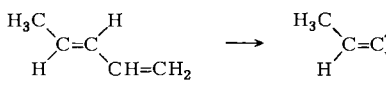
The regio- and stereochemistry of this reaction have been thoroughly examined[28, 30–34]. The reaction generally involves a *trans*-Markownikoff addition. However, with certain strained alkenes such as norbornene[32] and *trans*-cyclooctene and -nonene[35] *cis*-addition occurs. Substituted cyclohexenes give almost exclusively the axial alcohol[33, 34]. Optically active alcohols can also be obtained by employing chiral mercury(II) carboxylates[36, 37].

The oxymercuration-demercuration of dienes has proven quite interesting. The monohydration of unsymmetrical dienes can be accomplished using one equivalent of mercury(II) tri-



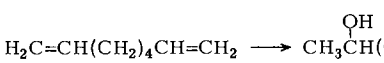
(22)

fluoroacetate [eq. (22)][38]. Fair yields of unsaturated alcohols can also be obtained from conjugated dienes [eq. (23)]. When



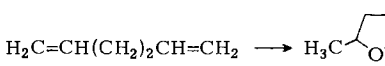
(23)

two equivalents of mercury(II) salt are employed, diols are obtained in high yields [eq. (24)], except in those cases where



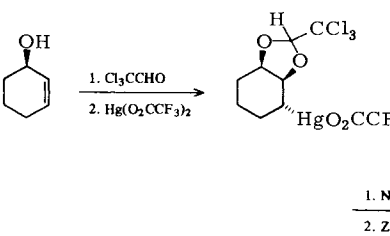
(24)

hydroxyl participation can result in the formation of tetrahydrofurans or tetrahydropyrans [eq. (25)][39]. These results are



(25)

best explained by two consecutive Markownikoff additions. Cyclic ether formation from dienes and unsaturated alcohols has been reported by a number of workers and can often proceed in high yield[40]. A number of interesting cyclic and polycyclic ethers have been prepared in this manner. One can take advantage of these reactions to convert cyclohexenols into *cis*-1,2-diols [eq. (26)][41].



(26)

Alkenes and dienes readily undergo alkoxymercuration-demercuration when an alcohol is used as the solvent [eq. (27)]. Although numerous β-alkoxymercurials have been pre-

pared using mercury(II) acetate[27], and some of these subsequently demercurated, mercury(II) trifluoroacetate appears to

$$RCH{=}CH_2 \xrightarrow[R'OH]{Hg(O_2CCF_3)_2} RCH(OR')CH_2HgO_2CCF_3 \xrightarrow[NaOH]{NaBH_4} RCH(OR')CH_3 \quad (27)$$

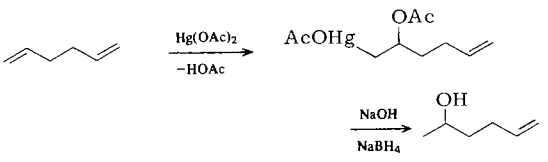
be a far superior reagent and, when employed in conjunction with an *in situ* alkaline $NaBH_4$ reduction, provides a very convenient route to highly branched ethers[42].

Peroxymercuration has also been achieved using mercury(II) carboxylates and both hydrogen peroxide and *tert*-butyl hydroperoxide [eq. (28)][43]. The alkyl *tert*-butyl peroxides can

$$RCH{=}CH_2 \xrightarrow[Hg(O_2CR')_2]{tBuOOH} RCH(OOtBu)CH_2HgO_2CR' \xrightarrow[NaOH]{NaBH_4} RCH(OOtBu)CH_3 \quad (28)$$

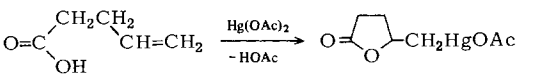
be demercurated with $NaBH_4$[44]. Cyclic peroxides can also be prepared from dienes by this approach[45].

Solvomercuration reactions can also prove useful for the synthesis of esters and lactones. In the absence of a protic solvent mercuric acetate will add directly to alkenes[46]. The monoaddition of mercury(II) acetate to dienes provides an improved method for the monohydration of symmetrical dienes [eq. (29)][47]. Both acyclic[48] and bicyclic[49] γ,δ-un-



(29)

saturated carboxylic acids form γ-lactones when treated with mercury(II) acetate [eq. (30)].



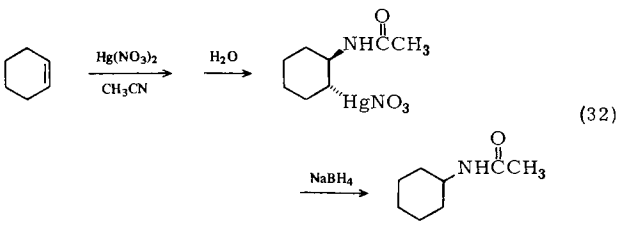
(30)

The aminomercuration of alkenes has been reported by a number of workers [eq. (31)][47, 50–52]. Both mercury(II)

$$RCH{=}CH_2 + 2\ HNR'_2 + HgX_2 \longrightarrow RCH(NR'_2)CH_2HgX \quad (31)$$

chloride and acetate, as well as primary and secondary alkyl and aryl amines, have been allowed to react with a wide variety of alkenes. The reaction has also been extended to the synthesis of heterocyclic amines by employing unsaturated amines and dienes[53, 54]. A variety of reducing agents have been used to reduce the mercurials[47, 51, 54, 55].

The amidomercuration of alkenes can readily be accomplished using mercury(II) nitrate and nitriles followed by hydrolysis[56, 57]. Reduction with sodium amalgam or $NaBH_4$ gives high yields of the corresponding amide [eq. (32)]. $LiAlH_4$ reduction gives the corresponding secondary amine[57].



(32)

A number of other mercury salts will also add across the double bonds of alkenes. In this manner β-azido[58], β-nitro[59], β-fluoro[60] and β-(trinitromethyl)[60] mercurials have been prepared.

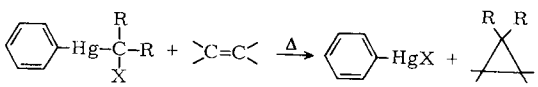
There are only a few examples of carbon-carbon bond formation *via* solvomercuration reactions[61]. Certain aromatic compounds react with alkenes in the presence of mercury(II) salts to give β-aryl alcohols or carboxylates, as well as 1,2-diarylalkanes. 1,3-Dicarbonyl compounds also undergo coupling with ethylene and mercury(II) salts.

The mercuration of alkynes has been much less thoroughly studied and appears rather limited in its synthetic utility[62]. Hydroxymercuration conditions provide a convenient method for the catalytic hydrolysis of alkynes to ketones. Alkoxymercuration generally produces ketals directly, although enol ethers have been obtained. Enol acetates can also be obtained if acetic anhydride is used as the solvent.

A few comments on the methods of demercuration should be made before concluding this section[63]. Although hydrazine has been employed as a reducing agent, it generally gives poor yields. $LiAlH_4$ has also been used, but offers no advantages over the widely used $NaBH_4$ procedure. This latter procedure usually proceeds in very high yield, although free radicals are involved and rearrangement products are sometimes observed[64]. On the other hand, sodium amalgam provides a valuable method for the stereospecific replacement of mercury by deuterium[65].

4. Carbene Transfer

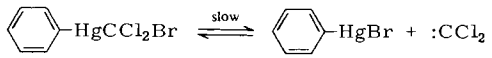
α-Halomethylmercury compounds have found extensive use in organic synthesis as carbene transfer reagents. They have proven particularly useful for the synthesis of cyclopropanes from alkenes [eq. (33)]. The utility of these compounds has



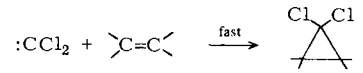
(33)

been extensively studied by *Seyferth et al.* and several reviews have appeared recently[66–68]. Rather than repeat those reviews, we shall primarily concentrate on the synthetic utility of these reagents, pointing out the advantages and disadvantages.

The majority of these carbene transfer reactions have employed phenyl(trihalomethyl)mercury compounds. In general, these reagents appear to reversibly dissociate "free"



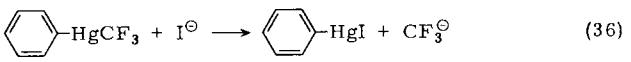
(34)



(35)

carbenes which then rapidly react with the alkene to generate cyclopropanes [eqs. (34) and (35)][69, 70]. Clean transfer of the more nucleophilic halide (I > Br > Cl) from carbon to mercury is observed in these reactions, apparently by a concerted intramolecular rearrangement[71]. The relative rates of reaction of various halomethylmercurials follow the same order (I > Br > Cl). Replacement of the phenyl group by a cyclohexyl group has also been observed to facilitate reaction[72].

Apparently, not all transfer reactions of this type proceed *via* a carbene intermediate however. For example, $(BrCH_2)_2Hg$ appears to involve a direct transfer of the CH_2 moiety from the mercurial to the alkene[73]. Under certain circumstances trihalomethyl carbanions can also be involved in these reactions. In those cases where the carbene is not readily thermally released by the mercurial, iodide ion can be employed to displace the trihalomethyl anion which subsequently decomposes to a carbene [eqs. (36) and (37)][74–76].



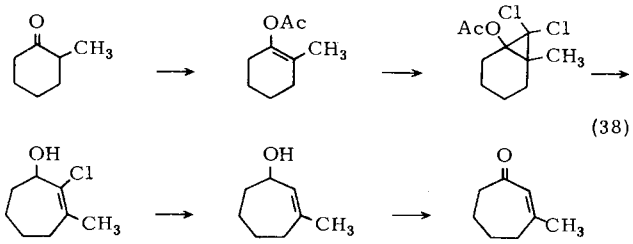
(36)

$$^{\ominus}CF_3 \longrightarrow :CF_2 + F^{\ominus} \qquad (37)$$

The α-halomethylmercurials have proven very valuable for the synthesis of cyclopropanes for a number of reasons. They proceed at reasonable temperatures under neutral reaction conditions, avoiding the introduction of strong bases or other potentially reactive reagents which are generally necessary for the formation of other transfer reagents. Thus, potentially serious side reactions between the actual carbene transfer reagent and reagents used to generate this species are avoided. Furthermore, the organomercurial reagent itself is generally inert to most substrates with which one desires to carry out a reaction. The phenylmercury(II) halide by-product in these reactions is also inert and usually precipitates from solution during reaction. It can also be easily reused in the preparation of additional transfer reagents. The insolubility of the resultant mercurial allows it to be removed from the cyclopropane product by simple filtration. These reactions can also generally be run in a variety of solvents. In general, one can employ an equimolar ratio of alkene and organomercurial and temperatures of 50—100 °C. Under these conditions simple alkenes give essentially quantitative yields. Those alkenes, such as ethylene, *trans*-stilbene, tetrachloroethylene, trimethyl(vinyl)silane and 3,3-dimethyl-1-pentene, which are generally unreactive towards other carbene reagents give satisfactory yields with the mercurial reagents. Alkenes, such as acrylonitrile, methyl acrylate and vinyl acetate which readily polymerize in the presence of base or reagents which generate the trihalomethyl carbanion, also give good yields with these reagents. A large number of functional groups are apparently accommodated by this reaction.

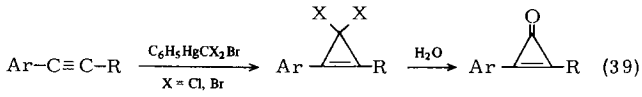
There are, however, several limitations to the use of these reagents. The most obvious one is the need to prepare and isolate the intermediate organomercurial. However, a number of literature procedures presently exist for the preparation of these compounds. The presence of certain functional groups in the alkene can also create problems. Carboxylic acids, alcohols and amines all react with these reagents. Reactions with a number of other functional groups can occur in the absence of carbon-carbon double bonds and a number of unusual heterocyclic compounds can be prepared in this manner.

These reagents have found other uses in organic synthesis as well. *Stork* has utilized dichlorocarbene additions to enol acetates as a means of ring expanding cyclic ketones to enones [eq. (38)][77].



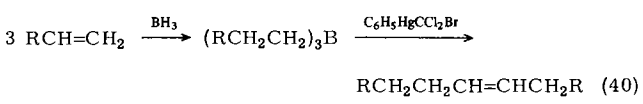
(38)

The addition of dihalocarbenes to arylacetylenes has provided a convenient route to aryl substituted cyclopropenones [eq. (39)][78, 79]. This reaction fails with dialkylacetylenes.



(39)

Organoboranes, derived from terminal alkenes *via* hydroboration, are readily coupled in good yield upon treatment with bromodichloromethyl(phenyl)mercury [eq. (40)][80].



(40)

Treatment of aldehydes and ketones with these same mercurials and triphenylphosphane provides an interesting route to a variety of vinyl halides [eq. (41)][81, 82]. This Wittig-like

$$R_2C{=}O + C_6H_5HgCHBr_2 + (C_6H_5)_3P \rightarrow R_2C{=}CHBr \qquad (41)$$

reaction quite likely proceeds through an intermediate phosphorus ylide.

All told, the halomethyl(phenyl)mercury reagents have proven extremely valuable for the synthesis of halocyclopropanes and exhibit a number of other interesting reactions which appear to possess considerable synthetic potential.

5. Halogenation of Organomercury Compounds

Organomercurials generally react quite readily with chlorine, bromine and iodine to give the corresponding organic halides [eqs. (42) and (43)]. This reaction has been widely

$$R_2Hg + X_2 \rightarrow RHgX + RX \qquad (42)$$

$$RHgX + X_2 \rightarrow HgX_2 + RX \qquad (43)$$

X = Cl, Br, I

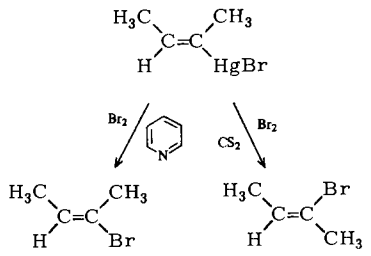
used to determine the position of the mercury atom in organomercurials. Synthetically, however, it is of rather limited importance since the usual starting materials for the preparation of organomercurials are either (1) organic halides themselves, (2) compounds derived from organic halides (organomagnesium or -lithium compounds), or (3) compounds readily halogenated directly (organoboranes, arenes, diazonium salts).

There are perhaps several noteworthy exceptions however. Several reports indicate that the halogenation of organomercurials prepared by solvomercuration reactions provides a convenient method for the synthesis of β-substituted organic halides [eq. (44)][83-87]. Equally valuable is the bromination

$$RCH{=}CH_2 \longrightarrow \underset{\displaystyle HgX}{\overset{\displaystyle Y}{RCH{-}CH_2}} \xrightarrow{X_2} \underset{\displaystyle X}{\overset{\displaystyle Y}{RCH{-}CH_2}} \qquad (44)$$

Y = –OH, –OR'; X = Br, I

of vinylmercury bromides which can apparently be controlled to give either the retained or inverted vinyl bromide simply by changing the solvent [eq. (45)][88]. The iodination of



(45)

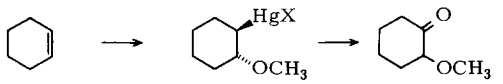
alkenyl-[89], alkynyl-[90,91] and arylmercurials[92] also appears to be of preparative utility.

It is interesting to note that the *in situ* iodination of *n*-alkylmercuric acetates derived from the mercuration of tri-*n*-alkylboranes gives the corresponding acetates and *not* the iodides, although the iodides are apparently intermediates in this reaction [eq. (46)][93]. *In situ* bromination provides the corresponding alkyl bromides[94].

$$3\ RCH{=}CH_2 \xrightarrow{BH_3} (RCH_2CH_2)_3B \xrightarrow[2.\ 3\ I_2]{1.\ 3\ Hg(OAc)_2} 3\ RCH_2CH_2OAc \qquad (46)$$

6. Oxidation and Sulfur Displacement Reactions

The large majority of organomercurials are very stable towards oxygen. On the other hand, organomercurials are readily oxidized by ozone[95]. Primary alkylmercurials give the corresponding carboxylic acid, plus all carboxylic acids possible from stepwise loss of carbon. Secondary organomercurials give good yields of ketones. This reaction would appear to be of value for the synthesis of α-substituted ketones from alkenes *via* solvomercuration-oxidation [eq. (47)]. Although



(47)

tertiary alkylmercurials yield the corresponding tertiary alcohols upon ozonolysis, this reaction is of little value due to the limited availability of these organomercurials.

The oxidation of either hydroxy- or methoxymercuration products with catalytic amounts of palladium(II) chloride and copper(II) chloride provides a very convenient method for

$$RCH{=}CH_2 \longrightarrow \underset{\displaystyle HgOAc}{\overset{\displaystyle OR'}{RCHCH_2}} \xrightarrow[3\ CuCl_2]{cat.\ PdCl_2} RCCH_3 \qquad (48)$$

the conversion of alkenes directly to ketones [eq. (48)][96]. If ethylene glycol is employed as the solvent the 1,3-dioxolane can be obtained directly [eq. (49)][97].

$$RCH{=}CH_2 \longrightarrow \underset{\displaystyle HgOAc}{\overset{\displaystyle OCH_2CH_2OH}{RCHCH_2}} \xrightarrow[3\ CuCl_2]{cat.\ PdCl_2} \underset{\displaystyle R}{\overset{\displaystyle O}{\overset{\displaystyle O}{\diagup\!\diagdown}}}\!\!CH_3 \qquad (49)$$

An analogous ketone preparation can be achieved by employing chromium trioxide and only a catalytic amount of mercury(II) acetate [eq. (50)][98]. This reaction presumably

$$RCH{=}CH_2 \xrightarrow[\substack{CrO_3/H_2SO_4\\ H_2O}]{cat.\ Hg(OAc)_2} RCCH_3 \qquad (50)$$

proceeds through intermediate β-hydroxy and β-keto mercurials. While the palladium reaction apparently gives good yields of ketones from internal olefins, the chromium trioxide procedure gives only 20—56% yields.

Arylmercurials have been oxidized in high yield to phenols by first treating with borane and then oxidizing the resulting arylborane [eq. (51)][99].

$$ArHgCl \xrightarrow{BH_3} [Ar{-}B\lessgtr] \xrightarrow[NaOH]{H_2O_2} ArOH \qquad (51)$$

Thermolysis of a large number of vinylmercury salts leads, often in high yields, to the corresponding vinyl oxygen and sulfur derivatives and metallic mercury [eq. (52)][100-106].

$$CH_2{=}CHHgX \xrightarrow{\Delta} CH_2{=}CHX + Hg \qquad (52)$$

X = $-\overset{O}{\overset{\|}{O}}CR$, –OAr, –SAr, –SR, –OTs, –SCN, $-S\overset{O}{\overset{\|}{C}}OR$,

$-OS(=O)_2-C_6H_4-CH_3$, $-ON{=}C(CF_3)_2$, $-OP(=O)(OR)_2$, $-OP(=O)(CH_3)OR$,

$-SP(=S)(OR)_2$, $-OSO_2F$

This reaction seems to be quite general and would appear to have some synthetic utility.

Diaryl sulfides can be prepared by heating diarylmercurials and sulfur to 190—250°C [eq. (53)][107-110]. At 140—180°C

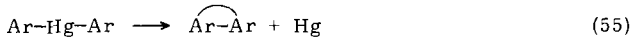
$$Ar{-}Hg{-}Ar \xrightarrow[190-250\,^\circ C]{S_8} Ar{-}S{-}Ar \qquad (53)$$

using either alkyl or arylmercury chlorides in sulfolane, good yields of the corresponding disulfides can be obtained instead [eq. (54)][111].

$$2\ RHgCl \xrightarrow[140-180\,^\circ C]{S_8} R{-}S{-}S{-}R \qquad (54)$$

7. Dimerization of the Organic Moiety of Organomercury Compounds

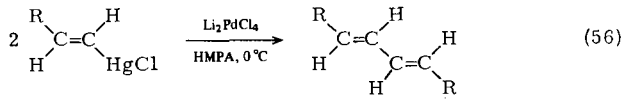
Transition metals have proven useful for the dimerization of a number of organomercurials. Dibenzylmercury and a number of diarylmercurials can be dimerized by heating with finely divided nickel, palladium, platinum, copper, gold or silver metals [eq. (55)][112]. Silver powder has been used to synthesize biferrocenyl[113], as well as biphenylene[114,115],



(55)

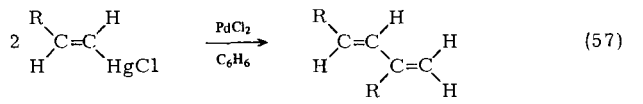
octafluorobiphenylene[116], benzo[*a*]biphenylene[117] and triphenylene[118] from cyclic arylmercurials.

Under certain conditions transition metal salts have also proven highly efficient for the dimerization of both aryl and vinylmercurials. Recently, several new procedures have been developed for the dimerization of vinylmercurials. We have observed that symmetrical 1,3-dienes and polyenes can be obtained in excellent yields by treating vinylmercury chlorides with lithium chloride and stoichiometric amounts of palladium chloride in hexamethylphosphoramide (HMPA) at 0°C [eq. (56)][119]. When benzene is used as the solvent an unusual



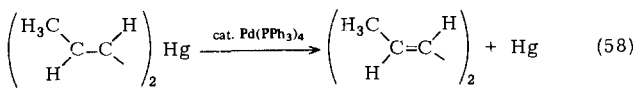
(56)

"head-to-tail" dimerization occurs instead [eq. (57)][120]. Catalytic procedures also exist for the symmetrical dimerization.



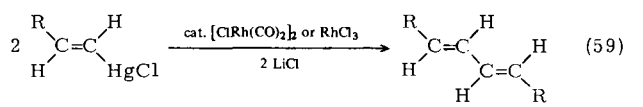
(57)

Thus, *Vedejs* and *Weeks* have reported that *cis*- and *trans*-dipropenylmercury are catalytically dimerized by *tetrakis*(triphenylphosphane)palladium(0) [eq. (58)][121]. More recently, we have



(58)

observed that rhodium(I) and rhodium(III) salts very efficiently catalyze the dimerization of both aryl and vinyl groups of organomercury chlorides [eq. (59)][122]. Palladium chloride



(59)

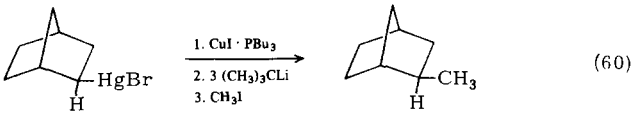
plus copper(II) chloride[123] or copper metal[124], or palladium acetate alone[125], have also been reported to dimerize arylmercurials. Surprisingly little use seems to have been made of any of these reactions for the synthesis of biaryls.

To date, alkylmercurials other than allylmercury iodide[119] and benzylmercurials[112, 119] have not been dimerized in good yield.

8. Reactions of Organomercury Compounds with Alkylating Reagents

In general, organomercurials are quite inert towards alkyl halides. Only under forcing conditions will arylmethyl halides alkylate dibutylmercury and arylmercurials[126–129]. The yields in these reactions are generally quite low. However, these reactions can be carried out at −15 to −20°C if aluminum bromide is added[130]. Diphenyl- and dibenzylmercury react with methyl iodide, ethyl bromide, chloromethyl methyl ether, benzyl bromide, *p*-nitrobenzyl bromide, and benzhydryl bromide to give low to modest yields of coupled products under these conditions. The highly reactive α-mercurated carbonyl compounds are readily alkylated at room temperature even in the absence of catalysts[131, 132].

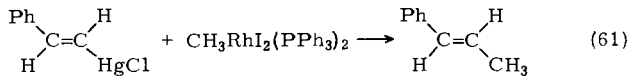
Transition metal reagents can also be used to promote alkylation. *Whitesides* has reported an interesting copper reaction which results in overall alkylation of an organomercurial [eq. (60)][133]. Unfortunately, this procedure appears to have



(60)

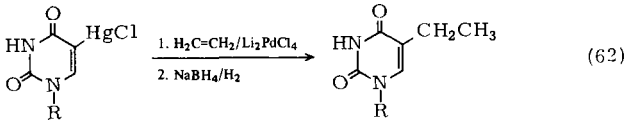
no advantages over the direct use of organocuprates since alkyl lithium reagents are required in both procedures.

Recently, we have observed that organorhodium(III) compounds will couple with both aryl- and vinylmercurials and we are presently studying the generality and synthetic utility of this reaction [eq. (61)][134].



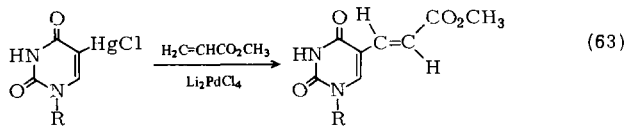
(61)

Bergstrom and *Ruth* have been able to alkylate, allylate and alkenylate 5-(chloromercury)nucleosides by taking advantage of previously reported organopalladium reactions [eq. (62)][135]. Use of allyl chloride gives the 5-allyl derivative



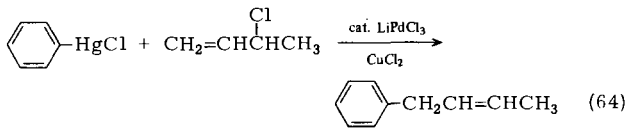
(62)

directly without reduction and methyl acrylate gives the 3-*trans* substituted propenoate [eq. (63)] (see Section 9).



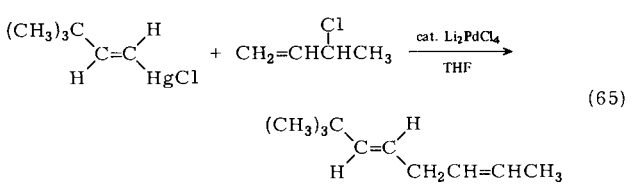
(63)

Both aryl- and vinylmercurials also undergo a smooth coupling with allylic halides when palladium chloride plus lithium chloride is employed as a catalyst. *Heck* reports that arylmercuric halides give 31—87% yields of allylaromatics [eq. (64)][136]. We have found that vinylmercurials give similar



(64)

yields of 1,4-dienes [eq. (65)][137]. It is especially noteworthy that both these reactions tolerate a number of functional



(65)

groups, occur at or below room temperature, and result in transposition of the double bond of the allylic halide. These reactions apparently proceed as indicated below [eqs. (66) to (68)].

$$RHgCl + PdCl_4^{2\ominus} \longrightarrow RPdCl_3^{2\ominus} + HgCl_2 \quad (66)$$

$$RPdCl_3^{2\ominus} + CH_2{=}CHCHCH_3 \longrightarrow \left[\begin{matrix} Cl_3Pd & Cl \\ RCH_2CH & CHCH_3 \end{matrix}\right]^{2\ominus} \quad (67)$$

$$\left[\begin{matrix} Cl_3Pd & Cl \\ RCH_2CH & CHCH_3 \end{matrix}\right]^{2\ominus} \longrightarrow RCH_2CH{=}CHCH_3 + PdCl_4^{2\ominus} \quad (68)$$

9. Alkene Substitution and Addition Reactions

In 1968 *Heck* reported a number of interesting reactions of organomercurials and alkenes promoted by palladium salts. Simple alkenes undergo vinylic hydrogen substitution reactions [eq. (69)][138]. In the reactions of alkenes containing

$$RHgX + PdX_2 + CH_2{=}CHY \rightarrow RCH{=}CHY \quad (69)$$

allylic hydrogens a mixture of isomeric substituted alkenes is obtained. These reactions are apparently limited to arylmercurials, alkoxycarbonylmercurials, and alkylmercurials which do not contain β-hydrogen atoms[138, 139]. A large number of functional groups are apparently accommodated by this reaction.

The reaction apparently involves the following sequence of reactions [eqs. (70) to (73)][140, 141]. When the original

$$RHgX + PdX_2 \longrightarrow RPdX + HgX_2 \quad (70)$$

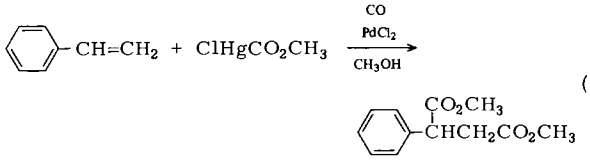
$$RPdX + CH_2{=}CHY \longrightarrow RCH_2\underset{\displaystyle PdX}{\underset{|}{C}}HY \quad (71)$$

$$RCH_2\underset{\displaystyle PdX}{\underset{|}{C}}HY \longrightarrow RCH{=}CHY + HPdX \quad (72)$$

$$HPdX \longrightarrow HX + Pd \quad (73)$$

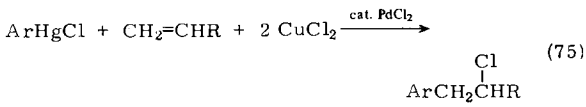
alkene contains allylic hydrogens, palladium hydride elimination can occur in more than one direction leading to an isomeric mixture. These reactions can be made catalytic in palladium if a reoxidant such as copper(II) chloride is employed to oxidize the palladium metal back to palladium(II).

The intermediate organopalladium addition compounds from the alkoxycarbonylmercurial addition reactions can be trapped by carbonylation, providing a novel synthesis of substituted succinic esters [eq. (74)][142].



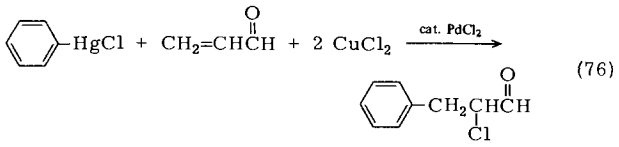
(74)

If the reaction of arylmercurials and alkenes is run in the presence of catalytic amounts of palladium chloride and



(75)

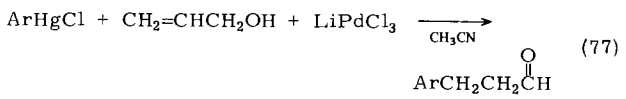
approximately 2 M copper(II) chloride, β-arylalkyl chlorides are produced instead [eq. (75)][143]. This reaction appears



(76)

valuable for the synthesis of α-halocarbonyl compounds [eq. (76)].

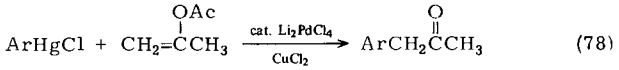
The reaction of primary and secondary allylic alcohols takes an entirely different course and produces 3-arylaldehydes and ketones respectively, although in low yield [eq. (77)][144].



(77)

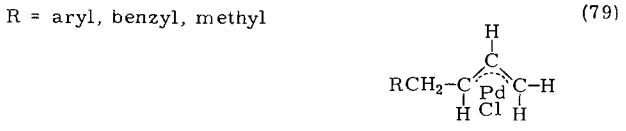
Apparently, the initial alkylpalladium compound obtained upon addition of the aryl palladium species to the carbon-carbon double bond preferentially eliminates a hydride from the carbon containing the hydroxyl group, producing an enol of the eventual carbonyl compound.

The reaction of enol esters provides 2-arylaldehydes and ketones, albeit generally in quite low yield [eq. (78)][145].



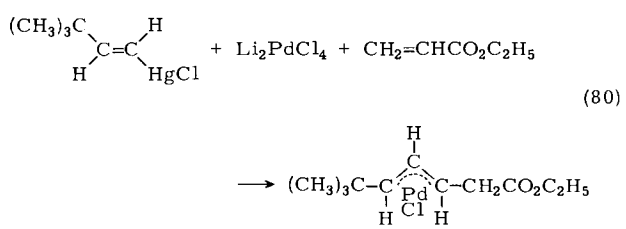
(78)

The reaction of organomercurials, palladium salts and conjugated dienes gives low to moderate yields of π-allylpalladium compounds [eq. (79)][146]. Quite surprisingly, the reaction



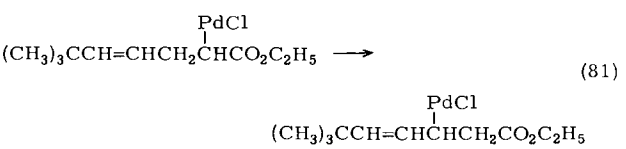
(79)

of vinylmercurials, palladium chloride and simple alkenes produces quite high yields of π-allylpalladium compounds also



(80)

[eq. (80)][147]. The π-allylpalladium compounds are apparently produced by a palladium hydride rearrangement [eq. (81)].



(81)

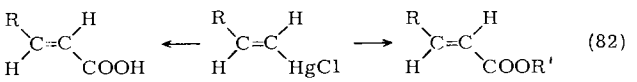
The palladium promoted addition of organic groups from organomercurials to carbon-carbon double bonds appears to be a very general reaction. The reactions also accommodate

a large number of functional groups. Unfortunately, however, they cannot be employed with organomercurials possessing β-hydrogens and many reactions give rather low yields. Nevertheless, the ease with which carbon-carbon bond formation occurs suggests considerable synthetic utility.

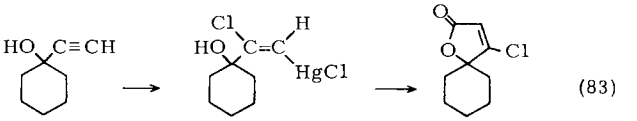
10. Carbonylation Reactions

The direct carbonylation of organomercurials by carbon monoxide is of limited synthetic utility[148-151]. It requires high temperatures and pressures and generally gives only very poor yields. However, palladium salts readily promote the carbonylation of organomercurials. For example, *Henry* has reported that ethylmercury(II) chloride reacts with palladium chloride and carbon monoxide at atmospheric pressure to give propionic acid upon aqueous workup[152]. Similarly, arylmercurials give acid chlorides in acetonitrile, esters in alcohol solvents, and anhydrides when palladium acetate is employed. Unfortunately, the yields are generally low.

On the other hand, vinylmercurials are readily carbonylated at low temperatures and one atmosphere carbon monoxide if lithium chloride and palladium chloride are used[153]. Depending on the solvent used, one obtains excellent yields of either α,β-unsaturated carboxylic acids or esters [eq. (82)].


(82)

These reactions can be accomplished with only catalytic amounts of palladium chloride or palladium on carbon, if copper(II) chloride is added as a reoxidant. These reactions have recently provided a novel new route to butenolides *via* carbonylation of the vinylmercurials derived from the addition of mercury(II) chloride to alkynyl alcohols [eq. (83)][17].


(83)

Diarylketones have also been obtained upon carbonylation of arylmercurials. Arylmercuric chlorides react with palladium chloride salts under 50 psig of carbon monoxide to give low yields of diaryl ketones[154]. Rhodium(I) and (III) complexes give somewhat better yields and can be run at atmospheric pressure. These reactions can be accomplished in considerably higher yield by using either tetracarbonylnickel[155] or octacarbonyldicobalt[156, 157]. The latter procedure can also be employed using only catalytic amounts of the carbonylmetal if the reaction is photolyzed [eq. (84)][158].

$$Ar_2Hg + CO \xrightarrow[h\nu]{\text{cat. } Co_2(CO)_8} Ar_2C{=}O + Hg \qquad (84)$$

11. Acylation of Organomercury Compounds

Most organomercurials are unreactive towards acid halides. However, a few arylmercury chlorides have been acylated to give the corresponding ketones [eq. (85)][128, 129]. α-Mercurated carbonyl compounds react readily with acid halides to produce the corresponding enol esters [eq. (86)][132].

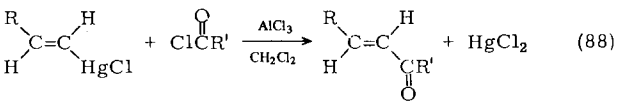
$$ArHgCl + ClCR \longrightarrow ArCR + HgCl_2 \qquad (85)$$

$$RCCl + ClHgCH_2CR' \longrightarrow CH_2{=}CR' + HgCl_2 \qquad (86)$$

Both $Pd[P(C_6H_5)_3]_4$[159] and aluminum halides[160, 161] promote rapid acylation of dialkyl- and diarylmercurials [eq. (87)], but it appears that only one of the two organic groups

$$R_2Hg + ClCR' \longrightarrow RCR' + RHgCl \qquad (87)$$

of the organomercurial reacts under these conditions. However, vinylmercury chlorides and aluminum trichloride react readily with acid chlorides to give excellent yields of α,β-unsaturated ketones with retention of configuration [eq. (88)][162].


(88)

12. Conclusion

Organomercurials have been known since 1850. They are now readily available by a number of routes and possess a number of characteristics which make them attractive as synthetic intermediates. Until lately, however, their low chemical reactivity has limited their use in organic synthesis. Recently, transition metal exchange reactions have been employed to promote a number of synthetically interesting reactions. These reactions appear to accommodate a large number of organic functional groups. However, the two most widely used reactions of organomercurials remain the carbene transfer reactions and solvomercuration-demercuration reactions.

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Solid Ionic Conductors: Principles and Applications

By Hans Rickert[*]

Solid ionic conductors, also called solid electrolytes, transport electric current by means of ions. The best known examples of these usually crystalline compounds include doped ZrO_2, as well as AgI, β-Al_2O_3, and CaF_2. Ionic conduction in solid electrolytes reaches its maximum value if a partial lattice of a solid compound undergoes transition at elevated temperature to a quasimolten state. The ionic conductivity in such solid compounds is then as high as in molten salts. Solid electrolytes have found many scientific and technological applications; thus, they can be used to study thermodynamic and kinetic problems, and to build fuel cells, batteries, sensors, and chemotronic components.

1. Principles

Solid ionic conductors are solid, generally crystalline, compounds in which electric current is carried by charged atoms, *i.e.* by ions. The passage of current is thus associated with mass transfer. Such ionic conductors are called "solid electrolytes", by analogy to liquid electrolyte solutions, and have permitted development of a new scientific discipline, *viz.* solid-state electrochemistry. The associated technology is termed solid-state ionics, in contrast to solid-state electronics.

The fact of ionic conduction in solids presents two sets of questions. First, how can ionic conduction arise microscopically at the atomic level, and how large can this ionic conduction become? Secondly, what applications are open to solid conductors in science and technology?

The first set of questions leads us to discuss disorder in solids. One limiting case is structural disorder—the quasimolten state—of a partial lattice of crystalline compound. This explains how the ionic conduction in certain solid electrolytes can become as high as that in concentrated electrolyte solutions or molten salts. However, unlike the liquid electrolytes, solid ionic conductors require no vessel to contain them, since they are still solid in spite of their quasimolten partial lattice. A solid ionic conductor can itself act as container or as the partition between electrode compartments; this leads to interesting constructional possibilities in the design of galvanic cells not provided by liquid electrolyte solutions or molten salts.

We thus come to the second set of questions, those concerning scientific and technological applications. The potential uses are largely based on the fact that solid electrolytes can be used to construct galvanic cells (also called elements) suitable for many different purposes; for example, not only for batteries or fuel cells but also for measurement or control engineering purposes, for display units, and for the developing field of chemotronic components. In the scientific area, galvanic cells containing solid electrolytes can be used in both thermodynamic and kinetic investigations. The importance of galvanic solid-state cells for thermodynamic investigations lies in the fact that their EMF provides information about chemical potentials or thermodynamic activities, partial pressures, and free energies. In kinetic investigations it is also important that reaction rates can be measured *via* the electric current in suitably constructed galvanic cells. The combination of rate measurement *via* an electric current with measurement of thermodynamic quantities *via* the EMF often permits analysis of kinetic processes. Both engineering applications and thermodynamic and kinetic studies will be illustrated in this

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review by typical examples. However, the theoretical principles underlying solid electrolytes will be considered first, and important solid ionic conductors surveyed. For further study the reader is referred to an introductory textbook[1] and to various reviews and conference proceedings[2-13].

1.1. Solid Electrolytes

The fact that solid substances, and in particular crystalline compounds, can act as ionic conductors has been known since the end of the last century. The atomistic interpretation of the possibility of ionic conduction in solids is also not new—it goes back to the twenties, to *Joffé*[14], to *Frenkel*[15], and to *Schottky* and *Wagner*[16]. Ionic conduction in solids is made possible by disorder in a crystal lattice, *i.e.* deviation from ideal order. At finite temperatures, unoccupied sites (vacancies) may occur in the crystal lattice, and/or additional particles may be present interstitially (interstitial atoms or ions) between the regular positions of the host lattice. Further defect centers may be due to foreign ions occupying interstitial sites.

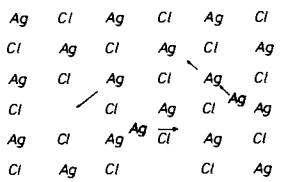


Fig. 1. Two-dimensional section through an AgCl crystal with lattice defects (schematic).

A possible defect is illustrated schematically in Figure 1 for silver chloride. The two-dimensional section through the silver chloride lattice shows silver and chlorine particles mainly in their normal positions. These particles have not been assigned any electric charge, because it is only meaningful to express charge relative to the unperturbed lattice, and silver and chloride ions in their normal sites are electrically neutral relative to the unperturbed lattice. The figure also shows two silver ions at interstitial sites; these ions bear an excess of positive charge. Two unoccupied sites can be seen, and these vacancies are charged negatively relative to the unperturbed lattice.

Possible transport mechanisms are also indicated in Figure 1 by arrows: a silver particle lying close to a vacancy may move into it. Moreover, the interstitial particles can change sites and thus bring about mass transfer. The concentrations of imperfection centers are subject to the laws of thermodynamic equilibrium, as demonstrated by *Frenkel*[15] and especially by *Wagner* and *Schottky*[16]. The concentrations of the various defects are related to one another by laws of mass action, just like the concentrations of ions on electrolytic dissociation in liquid electrolyte solutions. Thus, the treatment of imperfections can justifiably be compared with that of electrolytic dissociation. Disordered particles, and also vacancies, can be regarded as quasichemical species and have led to their own chemistry, called imperfection chemistry. Unfortunately, in the older and in the more recent literature different symbols are used for the imperfection centers, and the meanings attached to them are also different[17-20].

The concentrations of imperfection centers increase with rising temperature. The limiting case are crystals in which the concentrations of vacancies and interstitial particles become comparable; there then occurs a statistical distribution of particles in normal lattice positions and in interstitial positions. In this state it is no longer reasonable to distinguish between regular and interstitial lattice positions. The total number of possible positions for a single type of particle may be several times higher than the number of such particles in the crystal. This state is known as structural disorder (a partial lattice of the crystal is now quasimolten) and can be reached by a continuous process (CaF_2, see below) or by a discontinuous one (AgI). At 149 °C AgI passes from the β- into the α-phase, the iodide lattice changing into a cubic body-centered structure while the silver ions are distributed randomly between the iodide ions.

On the basis of X-ray structure analyses carried out by *Strock*[21,22], the silver ions in α-AgI were formerly assigned fixed positions over which they were distributed statistically (Fig. 2). Although there are 42 point positions for two silver

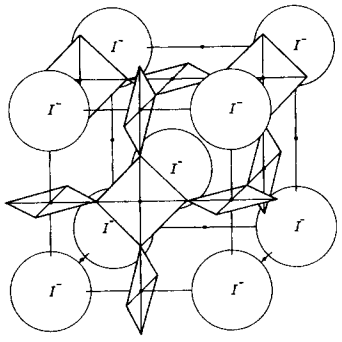


Fig. 2. Silver iodide lattice with the assumption of point sites for the silver ions (for two silver ions there are 42 point sites).

ions, the very size of these ions precludes independent occupation of all these positions. Discussion of the correlation factor for tracer diffusion in Ag_2S[23], which has a disorder analogous to that in AgI, as well as investigations by microwave techniques and by neutron scattering[24-27], have shown that it is more reasonable to speak of regions in which the silver ions engage in essentially random motion (Fig. 3).

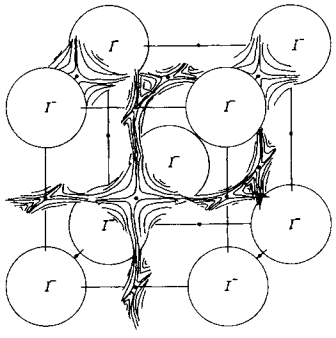


Fig. 3. Silver iodide lattice with the assumption of regions in which the silver ions can move.

The idea that the silver ions in α-AgI are already in a quasimolten state is supported by the diffusion coefficients, which are of the order $10^{-5}\,cm^2\,s^{-1}$ for a liquid, and by

thermodynamic values. The entropy for the transition from β-AgI to α-AgI amounts to $14.5\,JK^{-1}\,mol^{-1}$, the entropy of fusion to $11.3\,JK^{-1}\,mol^{-1}$. It is assumed that silver iodide melts in two stages. In the β→α transition the silver partial lattice passes into the quasimolten state (structural disorder), whereas the iodide partial lattice does not become liquid below the actual melting point. Comparable crystals that nevertheless do not show the special behavior of structural disorder before they actually melt have an entropy of fusion about as large as the sum of the transition entropy and entropy of fusion in AgI, *i.e.* about twice as large as the residual entropy of fusion in AgI. An analogous situation is found in some other crystalline compounds that contain a quasimolten partial lattice after passing through a transition point. This has been pointed out especially by *O'Keefe* and *Hyde*[28]. However, it should be mentioned that in all cases where an ordered state of one partial lattice is transformed into a disordered state, structural changes will also occur in the other partial lattice. It must remain an open question how the silver ions would behave if the iodide partial lattice of α-AgI remained unchanged at lower temperatures, *i.e.* if it were possible to supercool the α-AgI. It is conceivable that in this case the silver ions would become continuously more ordered as the temperature were lowered.

Compounds of another group (example CaF_2) undergo a continuous transition from the ordered to the strongly disordered state on heating. This continuous transition of a partial lattice into the quasimolten state without a change in the partial lattice of the other type of ion is also accompanied by characteristic thermodynamic properties: in the temperature region in which strong disorder develops, an abnormally high specific heat becomes evident[28]; thus, an increase in disorder requires the supply of additional energy.

In solid electrolytes with structural disorder not only are all the particles of one kind of ion mobile, so that they can all contribute simultaneously to current transport, but also their diffusion coefficient and thus their mobility attain values such as are found otherwise only in liquids or in gases compressed to the density of liquids. The ions thereby attain maximum limiting values not only for concentration but also for mobility, as determined by the nature of condensed systems. Thus, ionic conductors are optimized with respect to the partial conductivity of one type of ion, because the partial conductivity is governed by the relation:

$$\sigma_i = |z_i| F u_i c_i \qquad (1)$$

where z_i is the ionic valence, F Faraday's constant, u_i the electric mobility, and c_i the concentration of the mobile ions. If the concentration of the mobile particles c_i and their mobility u_i have reached their maximal values, then according to eq. (1) the partial conductivity σ_i also attains its maximal value. The high mobility and thus the high diffusion constant become intelligible within the atomistic picture if it is assumed that the ions hardly vibrate at all about their rest positions but instead move irregularly within the lattice with thermal velocities. Solid electrolytes containing structural disorder are often called "superionic conductors" or "optimized electrolytes".

Summarizing, it can be said that the possibility of ionic conduction in solids is due to disorder in the latter, and especially to the interstitial ions and vacancies. The disorder can become so great that the particles assume a random distribution and therefore behave like liquids, swimming in the space between the lattice sites of the other type of ion. Table 1 lists some solid electrolytes, but makes no claim to completeness if only because new electrolytes are currently being reported monthly and sometimes weekly. Figure 4 shows the conductivities of some important solid electrolytes as a function of the reciprocal temperature; the conductivity of concentrated sulfuric acid is included for comparison. It can be seen that the conductivity of solid electrolytes can lie in the same range as that of concentrated liquid electrolytes. For silver iodide, a solid electrolyte in which structural disorder sets in at a transition point, the conductivity jumps by about four orders of magnitude on transformation of the β- into the α-phase. In calcium fluoride, however, the conductivity rises continuously up to the melting point, but here undergoes no further change due to the melting process, *i.e.* at the melting point solid and liquid calcium fluoride have almost the same conductivity. In silver iodide the conductivity of the melt is actually slightly lower than the conductivity of the solid material shortly before the melting point.

Doped zirconium dioxide and thorium dioxide are important solid electrolytes which owe their conductivity to trans-

Table 1. Solid electrolytes. The ion named in the first column is that mainly responsible for the conductivity.

Conducting ion	Compound	Temperature range [°C]	Ref.
Oxide (O^{2-})	$ZrO_2(Y_2O_3)$	600–1600	[29]
	$ThO_2(Y_2O_3)$	600–1100	[30]
	$CeO_2(Gd_2O_3)$	500–1500	[65, 66]
Fluoride (F^-)	CaF_2	600–1400	[31, 32]
	NaF	330–980	[33]
	LiF	350–700	[34]
	PbF_2	200	[35]
	SrF_2	500–700	[36]
	BaF_2	500	[37]
Chloride (Cl^-)	$PbCl_2$	200–450	[38]
	$BaCl_2$	400–700	[37]
	$SrCl_2$	500–780	[39]
Bromide (Br^-)	$BaBr_2$	350–450	[37]
	$PbBr_2$	250–365	[38]
	KBr	605	[40]
Iodide (I^-)	PbI_2	255	[37]
	KI	610	[40]
Sodium (Na^+)	NaF	500	[33]
	NaCl	300–600	[33]
	NaBr	435	[41]
	$\beta\text{-}NaAl_{11}O_{17}$	20–700	[42]
	$Na_3Zr_2PSi_2O_{12}$	20–450	[43]
Silver (Ag^+)	α-AgI	150–450	[44, 45]
	β-AgI	100–140	[44, 45]
	AgCl	100–400	[46]
	AgBr	100–400	[47]
	Ag_3SBr	10–300	[48, 49]
	Ag_3SI	250–400	[50, 51]
	Ag_2HgI_4	50–100	[52–54]
	KAg_4I_5	20–220	[52–54]
	$RbAg_4I_5$	25–200	[52–54]
Copper (Cu^+)	β-CuI	369–407	[55, 56]
	CuCl	250–400	[55, 56]
	β-CuBr	385–469	[55, 56]
	γ-CuBr	250–385	[55, 56]
	$7CuBr\cdot C_6H_{12}N_4\cdot CH_3Br$	20–130	[57]
	KCu_4I_5	260–325	[58]
Lithium (Li^+)	$\beta\text{-}LiAl_{11}O_{17}$	25–800	[59]
	$LiI(Al_2O_3)$	25–100	[60]
	$Li_{0.8}Zr_{1.8}Ta_{0.2}P_3O_{12}$	25–200	[61]
Proton (H^+)	H_3OClO_4	−20–40	[62]
	$C_6H_{12}N_2\cdot 1.73\,H_2SO_4$	150–200	[63]

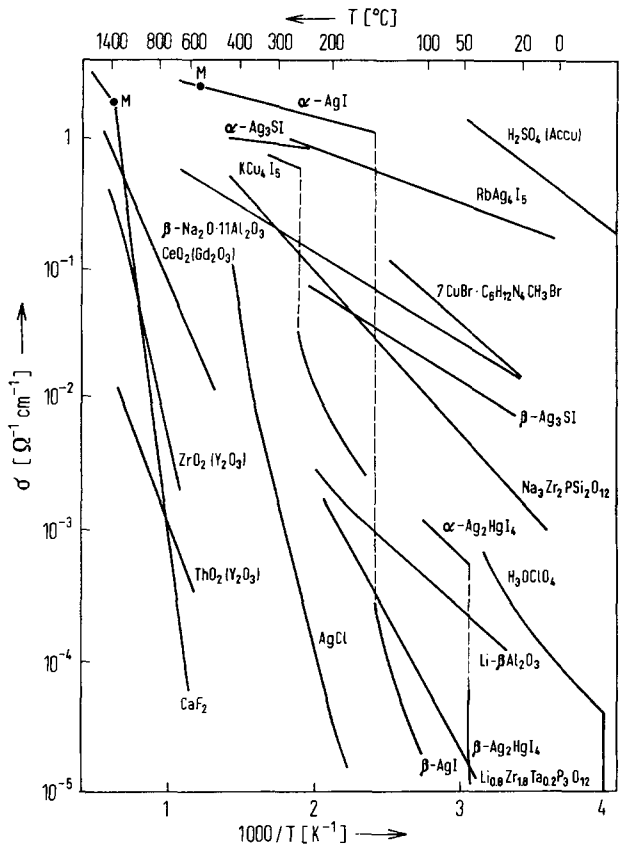


Fig. 4. Conductivity of important solid electrolytes (logarithmic) as a function of the reciprocal temperature (see Table 1). For comparison: conc. H_2SO_4 [64]. M = melting point.

port of oxygen ions. Recently, doped cerium dioxide has also been discussed for particular applications. Zirconium dioxide can be used between 600 and 1600 °C. It is also an interesting example of how high ionic conductivity can arise by processes other than those discussed above. The disorder centers responsible for the ionic conductivity of zirconium dioxide are charged oxygen ion vacancies. These are produced by dissolution of CaO, MgO, or Y_2O_3 in the zirconium dioxide. The calcium is incorporated at zirconium positions; since, however, only one oxygen ion is introduced with each calcium ion, one oxygen position remains unoccupied for each calcium atom introduced. The amount of doping is of the order of 10 mol-%; in this way it can be seen why doping produces a very large number of vacancies in the zirconium dioxide.

An important Na^+ ionic conductor is $Na_2O \cdot 11\,Al_2O_3$, so-called β-Al_2O_3. The mobile sodium ions are incorporated into the plane of the lattice and can therefore move only in two dimensions; polycrystalline material is used to obtain three-dimensional conductivity. $RbAg_4I_5$ and related compounds are interesting ionic conductors that display high ionic conductivity even at room temperature; in these materials the silver ions are mobile. They show structural disorder similar to that in AgI. $RbAg_4I_5$ has gained importance for manufacture of chemotronic components (see Section 2.4).

1.2. Galvanic Cells Embodying Solid Electrolytes

Galvanic cells can be set up with solid electrolytes just as with liquid ones, and therein lies their great importance. Their manifold applications will be discussed below with the aid of examples, but we shall first describe their most important properties. For this purpose we shall consider the galvanic cell represented schematically in Figure 5: it consists of doped

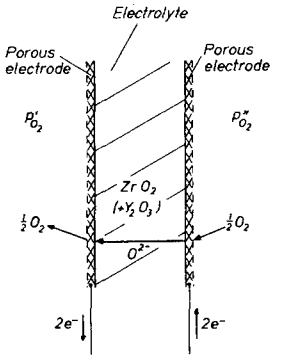


Fig. 5. Galvanic solid-state cell with zirconium dioxide as solid electrolyte and two oxygen electrodes with different oxygen partial pressures (schematic).

zirconium dioxide as the solid electrolyte with almost pure ionic conduction for oxygen ions. On the two sides there are porous, electronically conducting electrodes bathed in gaseous oxygen at different partial pressures. The zirconium dioxide must separate the electrode spaces from one another in gas-tight manner. For example, a tube of zirconium dioxide can be used that carries an electrode on the inner and another on the outer side, the outside and the inside being surrounded by gaseous oxygen at different partial pressures. If in the galvanic cell illustrated a positive electric current flows from the left to the right electrode, 1 mol of O_2 is transported from the right to the left electrode space by the passage of 4 faradays (4 F). The following cell reaction occurs:

$$O_2 \text{ (right electrode)} \rightarrow O_2 \text{ (left electrode)} \qquad (2)$$

The galvanic cell can thus be used as an oxygen pump if an external power source causes electric current to pass through the cell. It can, however, also act as a source of current, if different partial pressures of oxygen are maintained on the left and right. The electric work that in the reversible case of the galvanic element can be performed with the passage of 4 faradays amounts to $4EF$, where E is the EMF of the galvanic cell, defined as the electric potential of the right minus that of the left electrode. This work is equal to the negative free energy ΔG of cell reaction (2). We thus have:

$$\Delta G \text{ (cell reaction)} = -4\,EF \qquad (3)$$

ΔG can be expressed by the chemical potentials μ_{O_2} of oxygen, and we then have, for eq. (3), the following expression:

$$\mu_{O_2} \text{ (left electrode)} - \mu_{O_2} \text{ (right electrode)} = -4\,EF \qquad (4)$$

The chemical potential μ_{O_2} is connected with the oxygen partial pressure p_{O_2} by the following equation:

$$\mu_{O_2} = \mu^{\ominus}_{O_2} + R\,T \ln \frac{p_{O_2}}{p^{\ominus}_{O_2}} \qquad (5)$$

Here $\mu^{\ominus}_{O_2}$ denotes the standard chemical potential of oxygen, corresponding to a partial pressure $p^{\ominus}_{O_2}$ of 1 atm. R is the gas constant and T the absolute temperature. Substitution of eq. (5) into eq. (4) gives:

$$E = \frac{RT}{4F} \ln \frac{p_{O_2}\text{ (right electrode)}}{p_{O_2}\text{ (left electrode)}} \tag{6}$$

This shows a relation to exist between E, the EMF of the galvanic cell, and the ratio of oxygen partial pressures at the two electrodes. According to equations (4) to (6), the EMF of a galvanic cell thus contains valuable thermodynamic information. The EMF makes it possible to deduce the free energy of the cell reaction and the chemical potentials of the electrode components or the partial pressures of gases. For Figure 5, a particularly easily understood galvanic cell was chosen, with a very simple cell reaction. Cell reactions can, however, be of very varied types, according to the electrodes and the electrolytes used, and thus free energies could be and have been determined for many chemical reactions. This is illustrated in Section 3.2.2 by the formation of silver sulfide from silver and sulfur. Reaction enthalpies and reaction entropies can also be deduced from the temperature-dependence of the EMF.

However, galvanic cells are important not only for thermodynamic but also for kinetic studies. An electric current I passing through the cell shown in Figure 5 is a measure of the rate J at which oxygen is transported from right to left. The relation is:

$$J = I/(4F)\ [\text{mol/s}] \tag{7}$$

The transport of mass—in the form of ions through the electrolyte or of electrons through the external current circuit—can often be assigned to a chemical reaction or a transport process at an electrode. In this way reaction rates can be measured electrically (for examples see Section 3.2). It is often possible to analyze a reaction mechanism in detail by a combination of rate measurement by means of the electric current with measurement of thermodynamic quantities—in particular of chemical potentials—*via* the EMF of the galvanic cell.

2. Technological Applications of Solid Electrolytes

Solid electrolytes have recently required major technological importance. Four typical groups of application are discussed below as examples.

2.1. Sensors

Galvanic cells embodying solid electrolytes can be used for rapid, direct measurement of partial pressures in gases or of concentrations in liquids and melts. An especially important typical example is the cell, represented schematically in Figure 5, containing doped zirconium dioxide as the solid electrolyte. By using cells of this type a wide range of oxygen partial pressures in gases can be determined. The zirconium dioxide probe for such work is used at temperatures between about 500 and 1000 °C. In this temperature range zirconium dioxide becomes markedly electron-conducting only when the partial pressure of oxygen falls to about 10^{-16} atm, *i.e.* oxygen partial pressure can be measured with this probe down to such very low values. Such low partial pressures are of practical importance if, for example, mixtures of H_2/H_2O and CO/CO_2 or equilibria between metals and metal oxides are concerned. This wide range of oxygen partial pressures makes the zirconium oxide probe an excellent analytical instrument for measurements in gases. It should also be mentioned that the measured value is obtained very fast, indeed almost instantaneously. In such measurements a reference atmosphere, *e.g.* air or a metal/metal oxide mixture, is located on one side of the zirconium dioxide, so that the oxygen partial pressure is already known at one electrode; the oxygen partial pressure at the other electrode is then measured *via* the EMF in accordance with eq. (6). In the measurement the gas can be passed to the sensor. Commercial apparatus[67, 68] is available for measuring the oxygen content of *e.g.* highly purified inert gases.

Interesting applications lie in the field of medicine for studying the oxygen consumption in exhaled air, and in industry in the analysis of exhaust gases from furnaces or combustion engines. In such work it is often advisable to arrange the zirconium dioxide probe in the exhaust gas stream near the reaction space. Figure 6 shows such a probe that can be used for the control and regulation of the combustion process in Otto engines of motor vehicles[69]. This possibility of very exact control of gasoline/air mixtures is of particular interest in connection with the avoidance of air pollution.

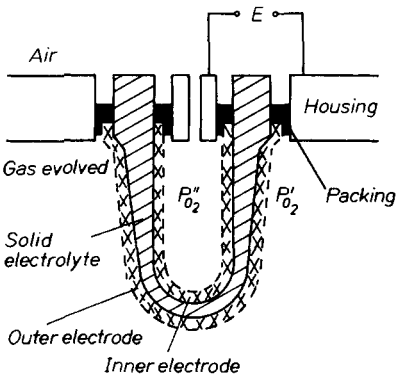


Fig. 6. Zirconium dioxide probe for the measurement of partial pressures of oxygen. The housing and packing are electrically conducting.

A similar probe can be used to measure the concentration or thermodynamic activity of oxygen in liquid metals. For example, the probe may be dipped in the melt during steel production; the direct display of the oxygen activity can be of appreciable advantage. If the range of oxygen pressure which can be measured is insufficient because of incipient electron conduction in zirconium dioxide, doped thorium dioxide can be used, which permits very much lower oxygen activities to be measured. By means of ThO_2 $(+Y_2O_3)$ the content of oxygen can be measured in, *e.g.* liquid sodium. The partial pressures of other gases, *e.g.* sulfur, can also be measured by sensors[70].

2.2. Fuel Cells and Electrolyzers

Figure 7 shows schematically the mode of operation of a high-temperature fuel cell incorporating zirconium dioxide

as the solid electrolyte. The zirconium dioxide in, *e.g.* tube or disk form, separates two electrode compartments, one containing air or pure oxygen and the other a fuel gas, *e.g.* hydrogen and carbon monoxide. The zirconium oxide carries two porous electrodes: nickel can be used on the fuel side, and on the oxygen side lanthanum-nickel oxide or some other electron-conducting oxide compatible with zirconium dioxide. The zirconium dioxide must be about 1 mm thick so that it can carry the electrodes. Other developments are in progress, to construct the zirconium dioxide as a thin-layer electrolyte, *i.e.* considerably thinner than 1 mm; mechanical strength of the cell must then be achieved in some other way, *e.g.* by strengthening the electrode.

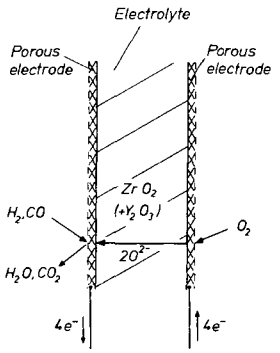


Fig. 7. High-temperature fuel cell (schematic).

In a high-temperature fuel cell the oxygen takes up electrons at one electrode, then migrates through the electrolyte as ions and combines at the other electrode with H_2 or CO to give H_2O or CO_2, respectively, whereby the electrons are given up and flow again to the other electrode in the external current circuit. In this way the desired energy is made available to the user. The advantages of the high-temperature fuel cell are that little or no polarization occurs at the electrodes and that high current densities can be achieved, *e.g.* 600 mA/cm^2 with a power density of 400 mW/cm^2. Difficulties arise with choice of the constructional material, and one disadvantage is that the cell can be heated only slowly to the working temperature. Further descriptions of high-temperature fuel cells, whose development is still in progress, are to be found in the literature[71-74].

By reversing the direction of the current flow in a high-temperature fuel cell, *i.e.* by supplying electrical energy in rather than removing it, steam can be decomposed and the cell can thus be used as an electrolyzer. The hydrogen produced can be stored or conducted by pipelines to remote sites where it can in turn serve for the production of energy on demand in a high-temperature fuel cell. This principle is being discussed in connection with large-scale energy storage and with the transport of energy. Other studies aim at decomposing steam and carbon dioxide in an electrolysis cell embodying zirconium dioxide so as to recover the oxygen from exhaled breath; this could be useful *e.g.* in manned spaceflight. The principle of the electrolysis cell can also serve for the purification of gases if it is desired to remove residual traces of oxygen, or for the deoxidation of liquid metals.

2.3. Solid-Electrolyte Batteries. Example: The Sodium-Sulfur Cell

The principle of a sodium-sulfur cell is shown in Figure 8. The solid electrolyte, an Na^+-ion conductor, consists of β-Al_2O_3 with the molecular formula $NaAl_{11}O_{17}$. It is generally used in the form of a tube closed at one end and filled with liquid sodium as the anode. An iron sponge, which absorbs

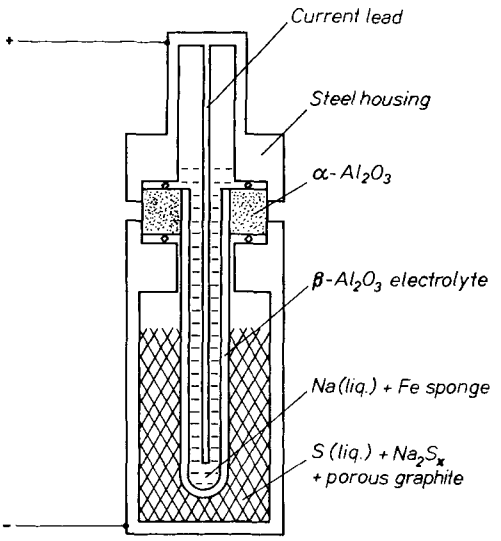


Fig. 8. Sodium-sulfur cell (schematic).

the liquid sodium, serves to improve the wetting of the electrolyte and at the same time to improve safety. A metal wire leads out of the cathode to carry the current. The cathode consists of liquid sodium polysulfide and sulfur in porous graphite. The working temperature of the sodium-sulfur cell is usually around 300 °C. In the cell reaction sodium ions pass through the electrolyte and electrons through the external circuit, so that sodium is dissolved in sodium polysulfide. In this way electrical energy can be liberated. The energy density of the sodium-sulfur cell is many times greater than that of the customary lead accumulators, and moreover, the materials needed for the electrolytes and electrodes are available in large quantities. The cell can be recharged by reversing the direction of the current. For all these reasons there is at present great interest in the sodium-sulfur cell. It is being discussed for large-scale energy storage and for electrotraction (for electric motor vehicles), and prototypes have already been built. Further details can be found in [75-77].

As well as the sodium-sulfur cell, cell systems have been developed with other solid electrolytes, some of these being characterized by very long lifetimes. Possible storage times of ten years and more have been reported; such lifetimes cannot be even approached with conventional batteries.

2.4. Chemotronic Components

Solid electrolytes or galvanic cells containing solid electrolytes, which find use in electrical circuits, are often called chemotronic components. Below we shall describe coulometers and time switches, analog memories, and capacitors containing solid electrolytes.

2.4.1. Coulometers and Time Switches

The galvanic cell

$Ag|RbAg_4I_5|Au$

can serve as a coulometer or time switch. The electrolyte $RbAg_4I_5$ is a good Ag^+-ion conductor even at room temperature. On passage of a current through this cell, silver is deposited in the gold electrode. The time switch is then in the loaded state. The silver can be transported back to the original silver electrode by a current flowing in the reverse direction. In this stripping process the cell potential is determined mainly by ohmic losses in the solid electrolyte. These losses depend on the current strength chosen and lie in the millivolt range. When all the silver has been stripped from the gold electrode the cell shows a sudden rise of potential, which can be used as a signal. Such electrochemical switches are suitable for times in the region of seconds to months. The $Ag|RbAg_4I_5|Au$ cell can also be used as a coulometer: the amount of current flowing during charging is then determined by the discharge process (for details see[78, 79]).

2.4.2. Analog Memories

The arrangement shown in Figure 9 has been proposed by *Takahashi* and *Yamamoto*[80] for use as an analog memory. The arrangement is symmetrical; on the outside there are two silver electrodes with a layer of the solid electrolyte $RbAg_4I_5$ on the inside of each; between these electrolyte layers is interposed a central electrode of silver selenide in which a small amount of silver phosphate has been dissolved. At

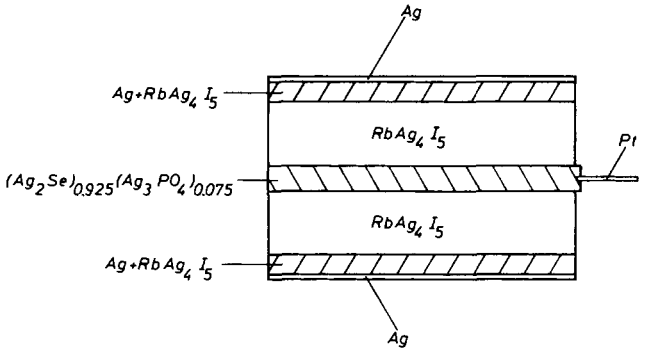


Fig. 9. Analog memory (schematic).

room temperature this solid selenide shows a remarkably high ionic conduction as well as a high electronic conduction. Current flowing over one-half of the arrangement can remove silver from this mixed-conductivity compound. The chemical potential of the silver in this selenide is thereby reduced and an EMF appears between the central electrode and the two outer electrodes. To avoid polarization effects, the EMF is measured against the silver electrode through which no current is flowing. The EMF changes continuously with the amount of charge that has passed, so that naturally more information can be stored than in the coulometers or time switches described above. Moreover, the reproducibility and accuracy of such devices are appreciably greater.

2.4.3. Capacitors Containing Solid Electrolytes

Capacitors can be built with $RbAg_4I_5$ as the electrolyte, one silver electrode, and an electrode of graphite and $RbAg_4I_5$; their capacities are of the order of 10 Faraday/cm^3, which is a thousand times larger than those of conventional capacitors, since here the capacity of the electrochemical double layer is utilized directly at the graphite/electrolyte interface. This interface can be made very large by intimate mixing of the substances concerned. However, the potential of a single cell is limited to 0.6 V, because the electrolyte begins to decompose at higher potentials. Possible applications of capacitors of this type are similar to those of the components described above, but in addition the capacitors have been discussed for energy storage because of their very high capacities.

3. Scientific Applications of Solid Ionic Conductors

Solid electrolytes can be utilized for both thermodynamic and kinetic investigations. This is illustrated below, again by means of selected examples.

3.1. Thermodynamic Applications

As discussed above, the EMF of galvanic cells containing solid electrolytes can be used for the determination of free energies, chemical potentials, partial pressures, or thermodynamic activities. By using the temperature-dependence of the EMF, information can also be obtained on the enthalpies and the entropies of the cell reactions. Consider, for example, the galvanic cell represented in Figure 10; it has been used by *Kiukkula* and *Wagner*[81] to determined the ΔG^0 for the

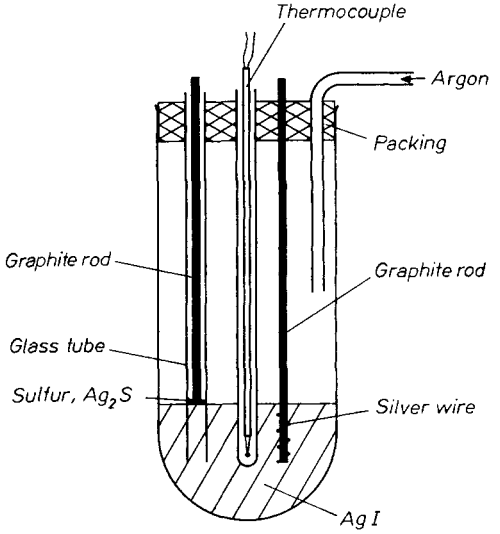


Fig. 10. Galvanic cell, C,Ag(solid)|AgI(solid)|Ag_2S(solid)S(liq.),C.

formation of Ag_2S. In these investigations AgI is first introduced into the apparatus in the form of a melt; after solidification, it serves as a solid electrolyte with almost pure Ag^+ ionic conduction. One electrode consists of a silver wire on a graphite shank, and the other electrode is a mixture of Ag_2S and sulfur, also on a graphite shank. On the passage of 2 faraday through the circuit from the silver electrode to the Ag_2S/sulfur electrode, the following reaction occurs:

$$2Ag + S = Ag_2S \quad (8)$$

Since all the reactants are present in their standard states, the cell EMF gives directly the standard Gibbs energy ΔG^0 (Ag_2S) for the formation of Ag_2S from silver and sulfur:

$$\Delta G^0(Ag_2S) = -2EF \quad (9)$$

In recent years a large number of other thermodynamic investigations have been carried out with solid ionic conductors. The reader is referred to the specialist literature[1, 11, 82] for further information.

3.2. Kinetic Investigations with Solid Ionic Conductors

In kinetic studies the measurement of the EMF of a suitably constructed galvanic cell is supplemented by measurement of the electrical current. How kinetic processes can be studied in this way will be discussed in the following Sections devoted to four selected examples.

3.2.1. Electrochemical Measurement of Oxygen Diffusion in Metals

The first kinetic investigation[83] with zirconium dioxide as the solid electrolyte was the determination of the diffusion coefficient D_O of oxygen in solid metals. The experimental arrangement is shown schematically in Figure 11. A silver

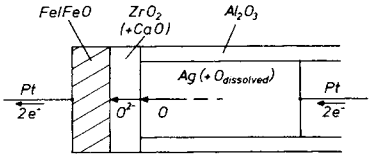


Fig. 11. Experimental arrangement for the electrochemical measurement of the diffusion of oxygen in solid silver (schematic).

cylinder was fused onto a zirconium dioxide tablet and surrounded on the outside by an Al_2O_3 tube to prevent radial diffusion of oxygen from the silver. Before the experiment the silver was saturated with oxygen and then formed an electrode in the galvanic circuit. The other electrode was a mixture of iron and ferrous oxide. As the current flows, oxygen ions move in the direction indicated by the arrows through the zirconium dioxide to the Fe/FeO electrode, where they are consumed by reaction with the iron. This consumption is compensated by oxygen which diffuses from the silver to the silver/zirconium dioxide phase boundary. The diffusion stream is thus converted into an electric current and so becomes accessible to measurement. Evaluation depends on the choice of the boundary and the initial conditions. Since the initial study, other diffusion measurements have been carried out, not only on metals but also on compounds[84–86].

3.2.2. Electrochemical Investigations of the Penetration of Silver through the Solid Silver/Solid Silver Sulfide Interface

The basic component of the experimental arrangement shown in Figure 12 is the solid-state cell

Pt,Ag(solid)|AgI|Ag_2S(solid),Pt

with AgI as an almost pure Ag^+ conductor. The difference from the arrangement in Figure 10 is that the Ag_2S is here not in equilibrium with the sulfur. The stoichiometry of the Ag_2S can thus be varied even if only within narrow limits, and so can the chemical potential of the silver in the Ag_2S. This cell exhibits two properties that are very important for

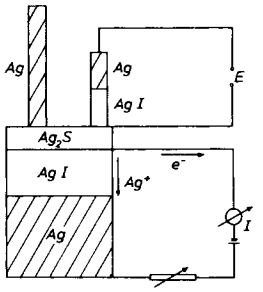


Fig. 12. Measurement arrangement for the electrochemical investigation of the passage of silver through the Ag/Ag_2S phase boundary.

the investigations concerned: first, a current passing through the cell, whose right-hand side is connected to the positive pole of an external power source, is a measure of the rate at which silver is removed from the Ag_2S, the silver ions dispersing through the AgI and the electrons through the platinum. Secondly, E, the EMF of the cell, depends on the chemical potential μ_{Ag} of the silver in the Ag_2S. When no current is flowing, we have:

$$\mu^0_{Ag} - \mu_{Ag} = EF \quad (10)$$

where μ^0_{Ag} denotes the chemical potential of pure silver and F is the Faraday constant.

Both possibilities were utilized in the experimental arrangement shown in Figure 12. The experiments were conducted in the temperature range of 200 to 400 °C[87, 88].

An Ag_2S tablet a few tenths of a millimeter thick rests on an AgI cylinder and this on a cylinder made of silver. The Ag_2S and the Ag are connected with platinum leads, so that a circuit is formed. The current in this circuit can be controlled by a resistor and measured by an ammeter. When a current flows, silver is removed from the Ag_2S and the chemical potential of the silver in Ag_2S falls continuously until finally sulfur is liberated (as sulfur vapor) from the Ag_2S unless further silver is added at the other side—which is accomplished through a silver rod standing on the Ag_2S tablet. In the steady state as much silver passes from the silver rod into the Ag_2S as is transported away through the AgI or the platinum in the form of silver ions and electrons. The steady state can be recognized by the fact that the chemical potential of the silver in the Ag_2S becomes constant. This potential can be measured by the Ag/AgI probe included in Figure 12. This probe produces a galvanic cell of the form Pt,Ag(solid)|AgI|Ag_2S(solid),Pt, whose EMF E according to eq. (10) is a measure of the difference between the chemical potentials of the silver in pure silver and in silver sulfide. In this way the measurements of current and potential are separated, and the potential measurements cannot be distorted by polarization phenomena. The probe thus corresponds to a Luggin capillary such as has long been used for studies on the electrochemistry of liquid phases. By using other special

probes it is also possible to measure electrochemical potential differences of silver ions and electrons and allow silver ions and electrons to pass separately through the phase boundary[89]. The results are important for understanding the reaction between silver and sulfur[88].

3.2.3. Electrochemical Investigation of Formation of Surface Layers on Metals; Example: Formation of Nickel Sulfide on Nickel at High Temperatures

The formation of nickel sulfide on nickel was investigated[90] with the aid of the experimental arrangement shown in Figure 13. Silver iodide was used as the solid electrolyte, being a

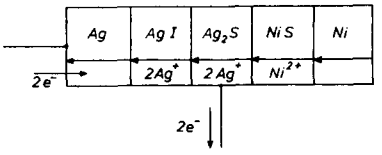


Fig. 13. Galvanic cell for the electrochemical investigation of the formation of NiS on nickel.

pure Ag^+ ionic conductor under the experimental conditions. The negative pole of a power source was connected to the left side of the arrangement and the positive pole to the right side. The galvanic cell itself consisted of tablets pressed together in a glass tube furnace flushed with nitrogen. As in the preceding example, an electric current passing through the cell is first of all a measure of the rate at which silver is removed from the silver sulfide, since silver ions migrate through the AgI and electrons through the external circuit. In this case, however, the rate of loss of the silver corresponds to the rate of the formation of nickel sulfide on nickel, since in this reaction nickel displaces the silver from the Ag_2S. The experiments were carried out in the galvanostatic and potentiostatic modes. The important quantities were again (a) the current, which is a measure of the reaction rate, here the formation of nickel sulfide, and (b) the cell EMF, which is not only a measure of the chemical potential of the silver in silver sulfide, but, in view of the Gibbs-Duhem equation, also a measure of the chemical potential of the sulfur in this compound and thus, because of the high mobility of the silver in Ag_2S, also a measure of the chemical potential of the sulfur at the Ag_2S/NiS phase boundary. In this way the parabolic constant k for the rate of formation of NiS on nickel at 400°C could be measured as a function of the chemical potential of the sulfur on the outside of NiS. The results provided information about the disorder in NiS.

3.2.4. Electrochemical Investigation of Evaporation Processes

We shall next consider, as an example, the evaporation of sulfur molecules from an Ag_2S surface into vacuum between 200 and 400°C[91].

The experimental arrangement shown in Figure 14 contains two cells of the type discussed in Section 3.2.2. A current flows through one of these cells. In the steady state the amount of sulfur evaporated from the silver sulfide surface and the amount of silver removed in the form of ions and electrons are equivalent. Once again, the steady state is recognizable by the fact that the chemical potential of the silver in the

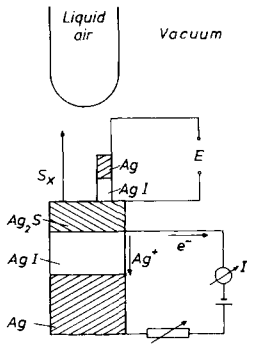


Fig. 14. Arrangement for the electrochemical investigation of the evaporation of sulfur from an Ag_2S surface into vacuum (schematic).

silver sulfide undergoes no further change and that E, the EMF of the second galvanic cell, remains constant. As was discussed in Section 3.2.3, this EMF provides a measure of the chemical potential of the silver and also of the sulfur in silver sulfide. In this way the rate of evaporation of sulfur can be measured as a function of the chemical potential of the sulfur in silver sulfide. The experimental arrangements are such that the evaporating sulfur, which is in vacuum, can be precipitated on a cold finger cooled with liquid air. Recent investigations[92] have shown that the evaporation coefficient for the evaporation of S_2 molecules from a sulfur surface is 0.5.

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COMMUNICATIONS

Communications are brief preliminary reports of research work in all areas of chemistry which, on account of its fundamental significance, novelty, or general applicability, should be of interest to a broad spectrum of chemists. Authors of communications are requested to state reasons of this kind justifying publication on submission of their manuscript. The same reasons should be clearly apparent from the manuscript. In cases where the editorial staff decide, after due consultation with independent referees, that these conditions are not met, manuscripts will be returned to the authors with the request to submit them for publication in a specialist journal catering for scientists working in the field concerned.

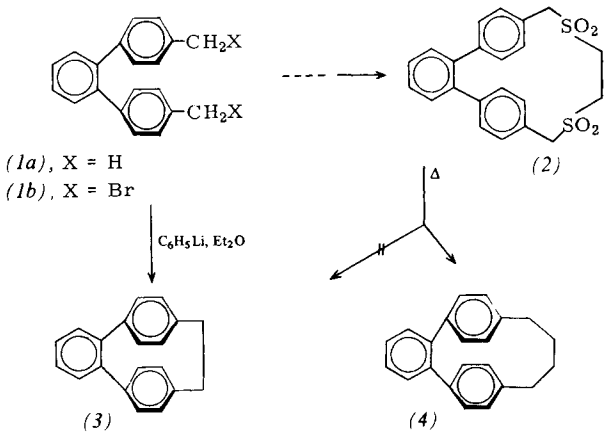
Cyclophanes Having Orthogonal Benzene Rings[**]

By *Neil Jacobson* and *Virgil Boekelheide*[*]

One of the attractions of cyclophane chemistry is that it provides compounds for which the spatial relationships are clearly defined by the rigid geometry of the molecule. Of particular interest are examples where benzene rings are held orthogonal to each other. In 1975, *Vögtle* and *Grütze*[1] reported that attempts to prepare [2](4',4'')orthoterphenylophane *(3)*, by the conversion of 4',4''-bis(bromomethyl)orthoterphenyl *(1b)* into the corresponding cyclic disulfone *(2)* followed by pyrolysis, did not give the desired *(3)*, but only [4](4',4'')orthoterphenylophane *(4)*.

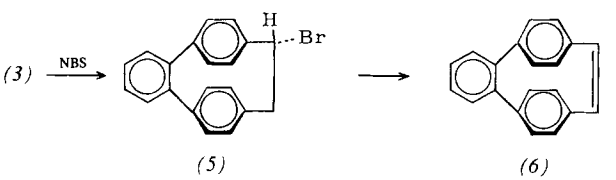
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Department of Chemistry, University of Oregon
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[**] This work was supported by the National Science Foundation.

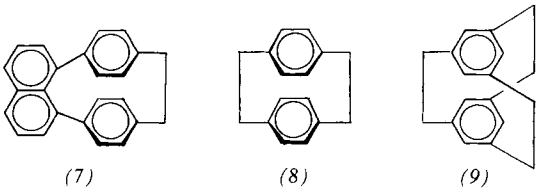


We now report that treatment of *(1b)* with phenyllithium in ether leads directly to the desired [2](4′,4″)orthoterphenylophane *(3)* in 22% yield, isolated after recrystallization from heptane as long white needles [m.p. 217—219 °C; NMR ($CDCl_3$): an AA′BB′ pattern centered at $\tau = 2.49$ (4H, *o*-ArH), a singlet at $\tau = 3.44$ (8H, *p*-ArH), and a singlet at $\tau = 6.89$ (4H, $ArCH_2$—)[2]].

Treatment of *(3)* with *N*-bromosuccinimide gives the corresponding monobromo derivate *(5)*, after preparative thin-layer chromatography over silica gel using a 1 : 9 mixture of benzene and petroleum ether (30—60 °C) for elution, as white crystals [m.p. 190—193 °C; NMR ($CDCl_3$): a multiplet at $\tau = 2.3$—2.8 (4H, *o*-ArH), a multiplet at $\tau = 3.2$—3.7 (8H, *p*-ArH), a multiplet at $\tau = 4.78$ (1H, $J = 7$ Hz, $J' = 9$ Hz, >CHBr), a multiplet at $\tau = 5.94$ (1H, $J' = 9$ Hz, $J'' = 14$ Hz, —CH_2CHBr), and a multiplet at $\tau = 6.68$ (1H, $J = 7$ Hz, $J'' = 14$ Hz, —CH_2CHBr)].



When *(5)* was warmed with potassium *tert*-butoxide in *tert*-butanol, it was readily converted in 75% yield into the corresponding olefin *(6)*, isolated after recrystallization from heptane as white platelets [m.p. 227—229 °C; NMR ($CDCl_3$): an AA′BB′ pattern centered at $\tau = 2.47$ (4H, *o*-ArH), a singlet at $\tau = 2.71$ (2H, —CH=CH—), and an AA′BB′ centered at $\tau = 3.40$ (8H, *p*-ArH).



In Table 1 the ^{1}H-NMR values for the bridging and *p*-phenylene protons of *(3)* and *(6)* are compared with those of some closely related cyclophanes *(7)*—*(9)*. As a general rule, the shorter the distance between decks in layered cyclophanes the higher the upfield chemical shift values for the attached aromatic protons. The upfield shift in going from the orthoterphenyl precursor *(1a)* to *(3)* and to *(6)* is relatively small. Presumably, this is due to the fact that the two *p*-phenylene rings of *(1a)* are forced to be parallel by steric constraints and, though still free to rotate, must rotate in a concerted fashion. Thus, fashioning a bridge across the C-4- and C-4″-positions of *(1a)*, as in *(3)* and *(6)*, does not markedly alter the geometry of these molecules from that of *(1a)* itself. The distance between decks in layered cyclophanes is affected both by the bond lengths in the bridges and the bond angles, with the latter usually being the most important. This is borne out in the comparison in Table 1 of *(6)* with *(3)* and with the naphthalene analog *(7)*[3]. However, the chemical shift values for the *p*-phenylene protons of *(6)*, *(3)*, and *(7)* show only small differences and are distinctly lower than for [2.2]paracyclophane *(8)*, where the distance between decks is known to be 3.14 Å[4], and very much lower than for the extreme example of [2.2.2](1,3,5)cyclophane *(9)*, where the average distance between decks is only 2.80 Å[5].

Table 1. Comparative ^{1}H-NMR data (τ values) of the compounds *(1a)*, *(3)*, *(6)*—*(9)*.

Cpd.	C—H (*p*-phenylene)	C—H (bridge)	Ref.
(1a)	3.28		
(6)	3.40	2.71	
(3)	3.44	6.89	
(7)	3.49	6.93	[3]
(8)	3.63	6.95	[6]
(9)	4.27	7.25	[7]

The ultraviolet absorption spectra of *(3)* and *(6)* show long wavelength absorption bands at 308 nm ($\varepsilon = 128$) and 307.5 nm ($\varepsilon = 134$), respectively. This is about the same as that observed for *(7)* and at slightly longer wavelength than that of [2.2]paracyclophane (302 nm, $\varepsilon = 96$). Thus, the experimental data for *(3)* and *(6)* suggest that there is very little, if any, interaction between the π-electron clouds of the orthogonal benzene rings.

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CAS Registry numbers:
(1a), 64586-14-7; *(1b)*, 55759-13-2; *(3)*, 64586-13-6; *(5)*, 64586-12-5; *(6)*, 64586-11-4; *(7)*, 61491-12-1; *(8)*, 1633-22-3; *(9)*, 27165-88-4

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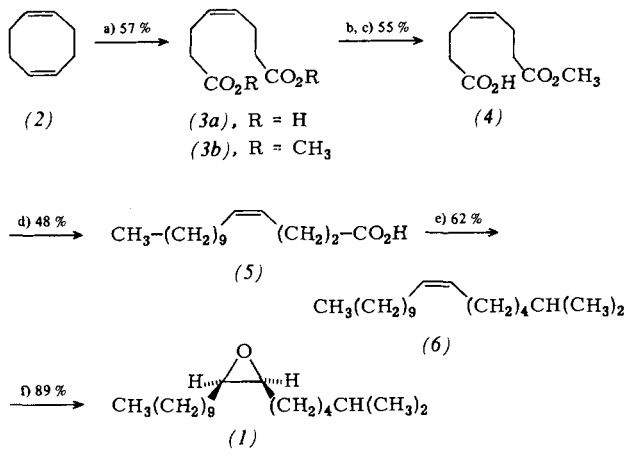
Synthesis of Disparlure by Kolbe Electrolysis[1]

By *Helmut Klünenberg* and *Hans J. Schäfer*[*]

Disparlure [(*Z*)-7,8-epoxy-2-methyloctadecane] *(1)*, the sex attractant of the gypsy moth *Lymantria dispar*[2], has been obtained stereoselectively containing various amounts of the (*E*) isomer by several synthetic pathways[2a, 3]. Since the attractant properties of synthetic pheromones may be greatly diminished by "contamination" with geometric isomers[4] we

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attempted to prepare configurationally pure *(1)*. Our aim was achieved by double Kolbe electrolysis starting from (*Z*,*Z*)-1,5-cyclooctadiene *(2)* (cf. Scheme 1).



Scheme 1. a) O_3; Jones reagent; b) MeOH, H^+; c) MeOH, KOH; H^+; d) $CH_3(CH_2)_7CO_2H$, Pt anode, MeOH; MeOH, KOH; H^+; e) $(CH_3)_2CH(CH_2)_2CO_2H$, Pt anode, MeOH; f) *m*-Cl—$C_6H_4CO_3H$.

Ozonolysis of *(2)*[5] and oxidative work-up with Jones reagent[6] afforded *(3a)* which was esterified to *(3b)* with methanol/sulfuric acid (cat.); *(3b)* was then partially hydrolyzed to *(4)* with methanolic potassium hydroxide. Separation of *(3b)* from *(4)* is possible by digesting the potassium salt of *(4)* with pentane, and that of *(4)* from *(3a)* by dissolution in carbon tetrachloride. A 1 : 10 mixture of *(4)* and pelargonic acid is 1 % neutralized and co-electrolyzed at 240 mA/cm^2. The symmetrical dimer of *(4)* is not formed; the Kolbe dimer of pelargonic acid is extracted from the potassium salt of *(5)* with light petroleum. Under the same conditions as *(4)*, but with 4-methylvaleric acid as co-reactant, compound *(5)* gives *(6)*, which can be separated from the symmetrical dimers by distillation. Compound *(6)* is epoxidized to *(1)*, whose structural data are in full agreement with those described in the literature[2, 3].

The monoester *(4)* is a suitable starting compound for the synthesis of other *Z*-configurated pheromones.

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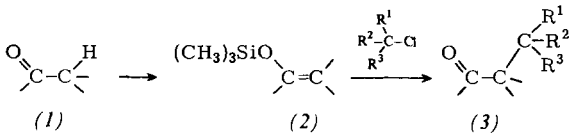
CAS Registry numbers:
(1), 29804-22-6; *(2)*, 1552-12-1; *(3a)*, 38561-68-1; *(3b)*, 54432-94-9; *(4)*, 64252-89-7; *(5)*, 64252-91-1; *(5)*, potassium salt, 64252-86-4; *(6)*, 35354-39-3; pelargonic acid, 112-05-0; 4-methylvaleric acid, 646-07-1.

[1] Pheromones, Part 3. This work was supported by the Arbeitsgemeinschaft Industrieller Forschungsvereinigungen e. V. and the Fonds der Chemischen Industrie.—Part 2: *W. Seidel, J. Knolle, H. J. Schäfer*, Chem. Ber. *110*, 3544 (1977).
[2] a) *B. A. Bierl, M. Beroza, C. W. Collier*, Science *170*, 87 (1970); b) J. Econ. Entomol. *65*, 659 (1972).
[3] *K. Eiter*, Angew. Chem. *84*, 67 (1972); Angew. Chem. Int. Ed. Engl. *11*, 60 (1972); *B. G. Kovalev, R. J. Ishenko, V. A. Marchenko, M. P. Filippova*, Zh. Org. Khim. *9*, 6 (1973); *H. J. Bestmann, O. Vostrowsky, W. Stransky*, Chem. Ber. *109*, 3375 (1976); *F. W. Küpper, R. Streck*, Z. Naturforsch. *B31*, 1256 (1976).
[4] *W. L. Roelofs, A. Comeau*, Nature (London) *220*, 600 (1968); *M. Jacobsen*, Science *163*, 190 (1969); the activity of *(1)* itself is not inhibited by its *E*-isomer [2a].
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[6] Oxidative work-up with Ag_2O/O_2 never gave more than 39 % of *(3a)*.

tert-Alkylation of Ketones and Aldehydes[**]

By *Manfred T. Reetz* and *Wilhelm F. Maier*[*]

Although the α-alkylation of carbonyl compounds *via* their corresponding bases is one of the most important C—C coupling reactions, it fails in the case of *tert*-alkyl groups. Thus on treatment with *tert*-alkyl halides, enolates or enamines yield practically only elimination or substitution products[1, 2]. We now present a simple solution to this problem[3] involving the use of Lewis acids:



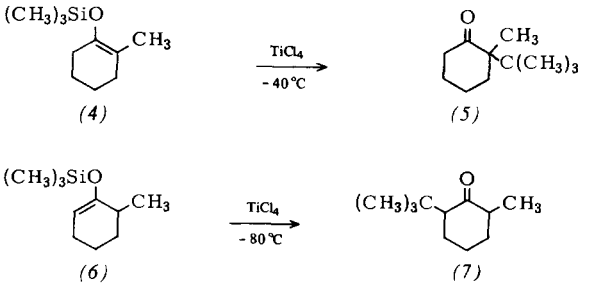
If the silylenol ethers *(2)*[4], which are easily obtained from ketones or aldehydes, are allowed to react with *tert*-butyl chloride in the presence of $TiCl_4$, $FeCl_3$, or $ZnCl_2$, the desired *tert*-butyl derivatives *(3)* are produced in good yields (Table 1). In the case of $TiCl_4$, optimum yields are obtained by using equimolar quantities of the Lewis acid in the temperature range −40 to −78 °C. Catalytic quantities of $FeCl_3$ or $ZnCl_2$ induce equally smooth conversions at room temperature.

Table 1. *tert*-Butylation of ketones and aldehydes.

Silylenol ether	Lewis acid	Product	Yield [%]
1-Trimethylsiloxy-cyclohexene	$TiCl_4$	2-*tert*-Butyl-cyclohexanone	85
	$FeCl_3$		70
1-Trimethylsiloxy-cyclopentene	$TiCl_4$	2-*tert*-Butyl pentanone	78
1-Trimethylsiloxy-6-methylcyclohexene	$TiCl_4$	2-*tert*-Butyl-6-methyl-cyclohexanone	67
1-Trimethylsiloxy-2-methylcyclohexene	$TiCl_4$	2-*tert*-Butyl-2-methyl-cyclohexanone	86
2-Trimethylsiloxy-3-methyl-2-butene	$TiCl_4$	3,3,4,4-Tetramethyl-2-pentanone	95
2-Trimethylsiloxy-propene	$ZnCl_2$ [a]	4,4-Dimethyl-2-pentanone	40
1-Trimethylsiloxy-1-butene	$ZnCl_2$ [a]	2-Ethyl-3,3-dimethylbutanal	30

[a] In these cases $TiCl_4$ is not very effective.

The alkylations proceed with a high degree of regiospecifity, *e.g.* the reactions of *(4)* and *(6)* give less than 5 % of the wrong isomer. The smooth conversion of *(4)* into *(5)* also underlines a further unusual feature of this procedure—namely the ready accessibility of compounds with two neighboring quaternary carbon atoms. The few methods so far known

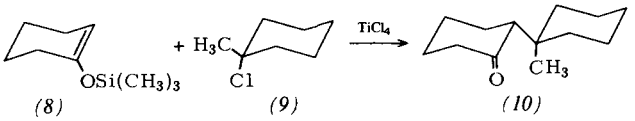


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for the synthesis of hexasubstituted ethanes involve several steps and usually give low yields due to steric factors[5].

The alkylation of *(8)* by *(9)* affording *(10)* (yield 45%) demonstrates that other *tert*-alkyl chlorides can also be used[6].



(8) *(9)* *(10)*

Synthesis of 2-tert-butylcyclopentanone

Titanium tetrachloride (20 g) in dichloromethane (30 ml) cooled to −45 °C is added under nitrogen within a period of 2 min to a mixture of 1-trimethylsiloxycyclopentene (15.6 g) and *tert*-butyl chloride (10.0 g) in dichloromethane (50 ml) at −45 °C. After stirring for 30 min, the mixture is diluted with CH_2Cl_2 (100 ml) and extracted with ice/water (500 ml). The aqueous phase is then washed with CH_2Cl_2 (2 × 100 ml). The organic phases are dried over magnesium chloride and the solvent evaporated off. 78% of the crude product (15 g) can be identified by gas chromatography as 2-*tert*-butylcyclopentanone. Fractional distillation affords 9.2 g (66%) of the pure compound, b.p. 95 °C/45 torr [^{1}H-NMR (CCl_4): τ = 9.0 (s, 9H), 8.4—7.5 (m, 7H)].

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CAS Registry numbers:
1-Trimethylsiloxycyclohexene, 6651-36-1; 1-trimethylsiloxycyclopentene, 19980-43-9; 1-trimethylsiloxy-6-methylcyclohexene, 19980-33-7; 1-trimethylsiloxy-2-methylcyclohexene, 19980-35-9; 2-trimethylsiloxy-3-methyl-2-butene, 17510-44-0; 2-trimethylsiloxypropene, 1833-53-0; 1-trimethylsiloxy-1-butene, 6651-33-8; 2-*tert*-butylcyclohexanone, 1728-46-7; 2-*tert*-butylcyclopentanone, 40557-24-2; 2-*tert*-butyl-6-methylcyclohexanone, 35579-35-2; 2-*tert*-butyl-2-methylcyclohexanone, 50336-92-0; 3,3,4,4-tetramethyl-2-pentanone, 865-66-7; 4,4-dimethyl-2-pentanone, 590-50-1; 2-ethyl-3,3-dimethylbutanol, 27919-27-3; *(9)*, 931-78-2; *(10)*, 64715-30-6; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; 2-methylcyclohexanone, 583-60-8; 3-methyl-2-butanone, 563-80-4; 2-propanone, 67-64-1; butanol, 123-72-8; *tert*-butyl chloride, 507-20-0; $TiCl_4$, 7550-45-0; $FeCl_3$, 7705-08-0; $ZnCl_2$, 7646-85-7.

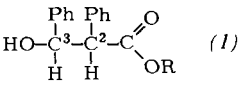
[1] *H. O. House*: Modern Synthetic Reactions, 2nd Edit. Benjamin, Menlo Park 1972, p. 533.
[2] The direct *tert*-alkylation of β-diketones under Friedel-Crafts conditions is worthy of note; normal ketones or aldehydes were not alkylated: *P. Boldt, H. Militzer, W. Thielecke, L. Schulz*. Justus Liebigs Ann. Chem. *718*, 101 (1968).
[3] An indirect method involving several steps is described by *E. J. Corey, R. H. K. Chen*, Tetrahedron Lett. *1973*, 3817.
[4] *H. O. House, L. J. Czuba, M. Gall, H. D. Olmstead*, J. Org. Chem. *34*, 2324 (1969).
[5] *M. J. Gibian, R. C. Corley*, Chem. Rev. *73*, 441 (1973); cf. *H.-D. Beckhaus, C. Rüchardt*, Chem. Ber. *110*, 878 (1977).
[6] Preliminary experiments show that alkyl halides of the allyl and benzyl types can be used in the same way.

Effect of Shift Reagents on NMR Coupling Constants

By *Geoffrey Brian Porter* and *Jon Simpson*[*]

Lanthanide shift reagents (LSR) are accepted as a standard aid in the interpretation of complex NMR spectra, but recent reviews[1] show that little has been reported on the variation of coupling constants as a result of the addition of such reagents. These reviews reveal that some workers have tried to relate a change in coupling constant to the inductive effect of the metal atom or conformational changes in cyclic systems. In the structural elucidation of flexible molecules the possible change in conformer populations must also be considered. This is particularly true when comparisons are made with X-ray diffraction results.

We wish to report a significant change in vicinal coupling constants observed during a study of the diastereomeric esters *(1)* derived from 2,3-diphenyl-3-hydroxypropionic acid. These esters have been characterized both chemically and by comparison of NMR spectra[2]. During the course of further ^{1}H-NMR measurements on these compounds, using [D_{27}]-Eu(fod)$_3$ and [D_{27}]-La(fod)$_3$, the values of J_{23} were found to vary as shown in Figure 1.



(1)

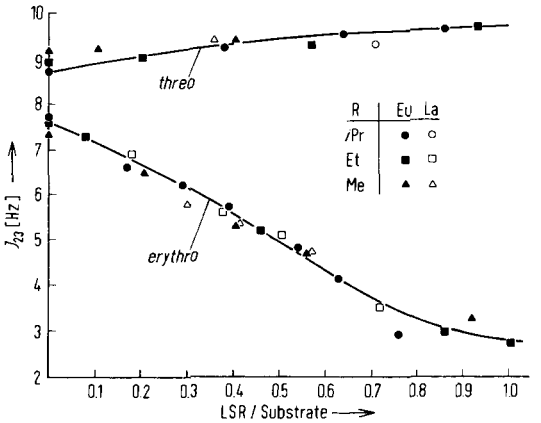


Fig. 1. Vicinal coupling constants (J_{23}) as a function of LSR/substrate ratio.

The initial values for J (no shift reagent present) correspond to a predominance of the rotamers T_A and E_A (cf. Figure 2, which shows the theoretical coupling constant for each rotamer calculated by the method of *Bothner-By*[3], using the appropriate electronegativities).

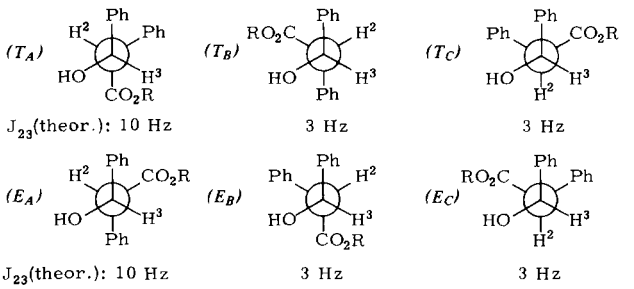


Fig. 2. *Threo* and *erythro* rotamers (*T*) and (*E*) of the diastereomeric esters *(1)*, and calculated J_{23} values.

When shift reagent is added, the chemical shift behavior is consistent with a 1:1 complex[4]. The most probable explanation for this and the results in Figure 1 is bidentate coordination of the shift reagent by both functional groups in the substrate. This can take place only if the groups are *gauche* to each other. Thus, in the *threo* series the shift reagent increases the population of (T_A) even further, so that J_{23} tends to the theoretical value for this rotamer alone. (T_B) is presumably excluded because of the presence of four adjacent

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bulky groups. In the *erythro* series, on the other hand, chelation requires an increase in the proportion of (E_B) or (E_C), and J_{23} progressively decreases to a limiting value which agrees closely with the calculated figure. Although both of these rotamers have four adjacent bulky groups, chelation with a lanthanide ion must be sufficient to overcome steric repulsion when there is no alternative.

Confirmation of this interpretation, based on chemical shift data, is available in work on other bifunctional systems[5]. However, direct evidence of bidentate coordination from suitable coupling constants has not hitherto been reported.

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CAS Registry numbers:
threo-(1) (R = *i*-Pr), 53697-64-6; *threo-(1)* (R = Et), 14367-00-1; *threo-(1)* (R = Me), 17226-93-6; *erythro-(1)* (R = *i*Pr), 53697-65-7; *erythro-(1)* (R = Et), 14367-01-2; *erythro-(1)* (R = Me), 17226-94-7; Eu(fod)$_3$, 17631-68-4; La(fod)$_3$, 19106-89-9

[1] *O. Hofer*, Top. Stereochem. *9*, 111 (1976); *I. O. Sutherland* in *L. M. Jackman*: International Review of Science, Org. Chem. Ser. 2, Vol. 1. Butterworth, London 1976; *J. Reuben*, Prog. Nucl. Magn. Reson. Spectrosc. *9*, Part 1 (1973).
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[5] *B. L. Shapiro, M. D. Johnston, M. J. Shapiro*, J. Org. Chem. *39*, 796 (1974); *J. W. De Boer et al.*, J. Magn. Reson. *25*, 437, 455 (1977).

Stretching Frequency and Force Constant of the Tungsten-Carbon Triple Bond[1]

By *Ernst Otto Fischer, Nguyen Quy Dao*, and *Wolfgang Rainer Wagner*[*]

In order to gain a further insight into the nature of the metal-carbon bond in carbyne complexes of transition metals[2] we have analyzed the IR and Raman spectra of *trans*-X(CO)$_4$W≡CCH$_3$ (X = Cl, Br, I) and *trans*-Br(CO)$_4$W≡CCD$_3$.

Figure 1 shows the Raman spectrum of the undeuterated bromo complex in the crystalline state; the spectra of the homologous chloro and iodo complexes exhibit the same characteristics.

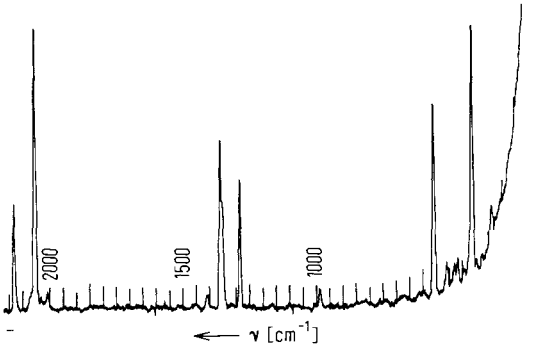


Fig. 1. Raman spectrum of crystalline *trans*-Br(CO)$_4$W≡CCH$_3$.

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Only two relatively intense bands appear at 1355 and 1282 cm^{-1} and a weaker one at 1409 cm^{-1} in the region expected for ν(W≡C) frequencies (800—1500 cm^{-1}). Since the weaker band is shifted to lower frequencies by deuteration it can be unequivocally assigned to the deformation mode $\delta_d(CH_3)$. The more problematic assignment of the two strong bands ν(W≡C) *versus* $\delta_s(CH_3)$ was accomplished by comparison with the spectrum of the analogous trideuteriomethylcarbyne complex. In this range, *trans*-Br(CO)$_4$W≡CCD$_3$ shows only one intense absorption in its solid-state Raman spectrum. The solution spectrum shows this band to be polarized and thus due to a totally symmetric vibration. We assign it to the stretching vibration of the tungsten-carbon triple bond.

In the undeuterated compound this vibration couples with the symmetric deformation vibration of the methyl group, occurring in the same region and belonging to the same symmetry class. As a result of Fermi resonance[3] two bands of similar intensity appear above and below (1355 and 1282 cm^{-1}) the frequency of 1315 cm^{-1} observed for the deuterated complex; they are both polarized in the same way and therefore are indeed a mixture of the normal modes δ_s(W≡C) and $\delta_s(CH_3)$.

The IR spectra (KBr) also show a strong band arising from a W≡C stretching mode (cf. Table 1).

Table 1. W≡C stretching vibration in X(CO)$_4$W≡CCR$_3$; limits of error: IR ±5 cm^{-1}; Raman (RA) ±2 cm^{-1}.

X	Cl		Br		I		Br	
R	H		H		H		D	
	RA	IR	RA	IR	RA	IR	RA	IR
	1361 1353 [a]	1355	1355 1347 [a]	1352	1358	1353		
							1315	1312
	1283	1272	1282	1274	1280	1276		

[a] These bands occur as double bands.

On comparison with the W≡N stretching vibration in the complexes $Cl_4WNC_2Cl_5$ and $Cl_3CCN(Cl_4)WNC_2Cl_5$[4] (intense band at 1286 cm^{-1}) the ratio of the frequencies ν(W≡C) : ν(W≡N) = 1.02 is of the same order as the theoretical frequency ratio of 1.074 calculated for a diatomic harmonic oscillator. According to our results based on a complete normal coordinate calculation, the value of 7.4 mdyn Å^{-1} is determined for the force constant of the W≡C bond.

Our results constitute independent proof of the metal-carbon triple bond in carbyne complexes deduced from previous X-ray studies.

Experimental

trans-Br(CO)$_4$W≡CCD$_3$: A sample of (CO)$_5$W=C(OCH$_3$)(CD$_3$)[5] (3.85 g, 10 mmol) is treated in the same way as the nondeuterated compound[6] with BBr_3 in pentane, and the product is purified by chromatography with CH_2Cl_2 on silica gel at −35 °C. After recrystallization and drying *in vacuo* at −10 °C the bromocarbyne complex is obtained as colorless crystals. Yield 2.6 g (65 %).

The Raman spectra (Coderg PH 1 with He-Ne laser, Spectra Physics Model 125) were recorded in the solid state at −196 °C or in solution (CH_2Cl_2) at −25 °C.—The IR spectra were recorded at room temperature (Beckman IR 10).

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CAS Registry numbers:
Br(CO)$_4$W≡CCH$_3$, 50726-31-3; Cl(CO)$_4$W≡CCH$_3$, 50726-30-2; I(CO)$_4$W≡CCH$_3$, 50726-32-4; Br(CO)$_4$W≡CCD$_3$, 64784-32-3; (CO)$_5$W=C(OCH$_3$)(CD$_3$), 64784-31-2; BBr_3, 10294-33-4

[1] Transition Metal Carbyne Complexes, Part 35.—Part 34: *E. O. Fischer, S. Walz, W. R. Wagner*, J. Organomet. Chem. *134*, C 37 (1977).
[2] Review: *E. O. Fischer, U. Schubert*, J. Organomet. Chem. *100*, 59 (1975).
[3] *G. Herzberg*: Molecular Spectra and Molecular Structure, Vol. II. Van Nostrand, New York 1964, p. 215.
[4] *M. B. G. Drew, K. C. Moss, N. Rolfe*, Inorg. Nucl. Chem. Lett. 7, 1219 (1971).
[5] *C. G. Kreiter, E. O. Fischer*, Chem. Ber. *103*, 1561 (1970).
[6] *E. O. Fischer, G. Kreis, C. G. Kreiter, J. Müller, G. Huttner, H. Lorenz*, Angew. Chem. *85*, 618 (1973); Angew. Chem. Int. Ed. Engl. *12*, 564 (1973).

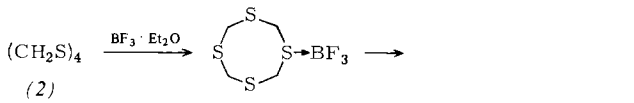
Copolymerization of Tetrameric Thioformaldehyde with Oligomeric Thioformaldehydes, Substituted Analogs, or Sulfur

By *Max Schmidt* and *Eckhard Weissflog*[*]

In acid solution, hydrogen sulfide and formalin afford trimeric thioformaldehyde $(CH_2S)_3$ [1,3,5-trithiane *(1)*] as well as polymethylene sulfides $(CH_2S)_n$. The latter products are not thermoplastic; their melting or decomposition temperatures depend upon the conditions of their preparation and vary between 160 and 220 °C[1]. The trithiane *(1)*, the oligomeric thioformaldehyde having the highest melting point (*ca.* 215 °C), can be polymerized only under relatively drastic conditions[2]. This also applies to the substituted trithianes we have prepared so far and to some substituted tetrathiocanes[3].

In contrast, it proves much easier to convert tetrameric thioformaldehyde $(CH_2S)_4$ [1,3,5,7-tetrathiocane *(2)*] and the next higher homolog $(CH_2S)_5$ into polymethylene sulfide, which is highly crystalline up to its relatively sharp melting point (without decomposition) of *ca.* 240 °C, by treatment with boron trifluoride-diethyl ether[4].

We have now found that the highly reactive intermediate *(3)* (diradical or zwitterion?) presumably formed from boron trifluoride-diethyl ether and the tetrathiocane *(2)* according to



(2)

$$CH_2\text{–}S\text{–}CH_2\text{–}S\text{–}CH_2\text{–}S\text{–}CH_2\text{–}S\text{–}BF_3$$

(3)

is able to attack trithianes including *(1)*, substituted tetrathiocanes, and elemental sulfur (as well as elemental selenium, albeit less effectively) in such a way that copolymers with interesting properties are formed under mild conditions. For instance, an equimolar mixture of *(1)* and *(2)* reacts with $BF_3 \cdot Et_2O$ at *ca.* 100 °C to give a practically quantitative yield of a polymethylene sulfide mixture which melts without decomposition between 245 and 265 °C. Even at a molar ratio of *(1)* to *(2)* of 4:1 the polymeric product $(CH_2S)_n$ is still formed in 87 % yield (although only at *ca.* 150 °C owing to the higher melting point of the starting mixture).

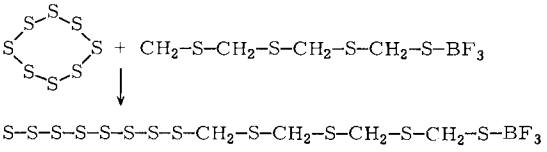
The oligomeric thioformaldehydes form silver complexes which can be utilized for their separation[5]. The granular polymer from the above reaction complexes Ag^+ ions from aqueous solution. These ions can be eluted with aqueous NH_3 to regenerate the pure polymer.

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We have already substituted the carbon atom of *(1)* and *(2)* to varying degrees on a previous occasion (R = CH_3, $Si(CH_3)_3$, $Ge(CH_3)_3$, $Sn(CH_3)_3$, or COOH instead of H)[3]. Like pure *(1)*, these derivatives also undergo BF_3-catalyzed copolymerization with *(2)*. The original substitution pattern is rediscovered at the carbon atoms of the C—S—C chains, modified according to the ratio of the reactants.

The properties of the new polymers are expectedly influenced by the substituents. They usually have wide melting ranges and some of them are thermoplastic. Those containing carboxyl groups are suitable for use as ion exchangers (the ion selectivity has yet to be investigated).

Oligomeric thioformaldehydes and elemental sulfur form homogeneous melts whose physical properties deviate considerably from those of pure sulfur. Treatment of a molten mixture of *(2)* and S_8 with $BF_3 \cdot Et_2O$ results in extensive incorporation of sulfur into the insoluble polymeric product. Once again the reactive intermediate *(3)* will first be formed and open the sulfur rings in a subsequent step:



Procedures (typical examples)

a) Compounds *(1)* (1.38 g, 0.01 mol) and *(2)* (1.84 g, 0.01 mol) are mixed together and melted. The clear homogeneous melt solidifies within seconds on addition of a small drop of $BF_3 \cdot Et_2O$ at *ca.* 100 °C. The brittle polymer is ground mechanically and extracted for 8 h with benzene, whereupon 0.13 g of *(1)* dissolves. Yield of $(CH_2S)_n$: 3.09 g (96 %). The almost colorless product forms a clear melt between 260 and 265 °C; at slightly higher temperature it decomposes slowly with evolution of gas.

b) Compound *(2)* (1.84 g, 0.01 mol) and 1,3,5,7-tetrathiocane-2-carboxylic acid[3b] (2.28 g, 0.01 mol) are suspended in xylene (10 ml) and heated to boiling. After addition of a drop of $BF_3 \cdot Et_2O$ the mixture is filtered. The solid residue is washed several times with hot benzene, then with concentrated NH_3 solution, and finally with dilute hydrochloric acid. The dried colorless finely crystalline product melts between 160 and 200 °C, decomposition with evolution of gas being observed at 180 °C. Yield of $[-(CH_2S)_7-CH(COOH)-S-]_n$: 1.73 g (42 %). One carbon atom in eight in the C—S—C chain bears a carboxyl group.

c) Compound *(2)* (0.92 g, 5 mmol) and S_8 (0.64 g, 2.5 mmol) are melted together (*ca.* 95 °C) to form a pale yellow mobile liquid. At 110 °C a drop of $BF_3 \cdot Et_2O$ is added and the mixture stirred mechanically. Polymerization is complete within about 15 s. The cooled brittle mixture is ground and extracted with benzene for 48 h. Mainly cyclooctasulfur crystallizes from the extract. The almost colorless polymer melts with partial decomposition at 146—149 °C. Yield: 1.22 g (78.2 % for $(CH_2S_2)_n$). Thus about half of the sulfur is incorporated into the insoluble polymer.

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CAS Registry numbers:
(1), 291-21-4; *(2)*, 2373-00-4; *(3)*, 65150-28-9; $(CH_2S)_n$, 30699-99-1; S_8, 10544-50-0; 1,3,5,7-tetrathiocane-2-carboxylic acid, 58925-90-9; $[-(CH_2S)_7-CH(COOH)-S-]_n$, 65149-93-1; $(CH_2S_2)_n$, 65149-94-2.

[1] Literature survey: *P. Kochendörfer*, Dissertation, Universität Marburg 1964.

[2] *J. I. Takeda, K. Hayashi, S. Okamura*, J. Appl. Polym. Sci. *13*, 1435 (1969); *R. C. Gearhart, J. M. Schultz*, Makromol. Chem. *177*, 835 (1976).
[3] a) *M. Schmidt, E. Weissflog*, Z. Anorg. Allg. Chem. *418*, 208 (1975); b) Chem. Ber. *109*, 1239 (1976).
[4] *M. Schmidt, K. Blaettner, P. Kochendörfer, H. Ruf*, Z. Naturforsch. *B21*, 622 (1966); *M. Russo et al.*, J. Polym. Sci. *B3*, 455, 501 (1965); *E. Weissflog*, Dissertation, Universität Würzburg 1974.
[5] *M. Schmidt, E. Weissflog*, Z. Anorg. Allg. Chem. *406*, 271 (1974).

$[Au_2(WS_4)_2]^{2-}$, A Novel Inorganic Ring System

By *Achim Müller, Horst Dornfeld, Gerald Henkel, Bernt Krebs*, and *M. P. A. Viegers*[*]

Whereas thioheteroanions, containing a transition element with an open d shell as central atom can be classified from the structural point of view according to the rules of classical complex chemistry[1], unexpected and interesting coordination is found in those thioheteroanions which contain only metal atoms with closed d shells, such as $[Sn_2(WS_4)_2]^{4-}$[2].

We have now isolated a cyclic thioheteroanion as the salt $[(C_6H_5)_4P]_2[Au_2(WS_4)_2]$ *(1)* in the form of dark red crystals by reaction of $[Au(S_2O_3)_2]^{3-}$ with WS_4^{2-}. Compound *(1)* could be characterized by elemental analysis and X-ray structure analysis, as well as by ^{197}Au Mössbauer and vibrational spectroscopy.

The structure of the new gold(I) compound was determined from single crystal diffractometer data ($R = 6.9$ %). *(1)* crystallizes in the triclinic space group $P\bar{1}$ with the unit cell constants $a = 12.871(3)$, $b = 11.197(3)$, $c = 11.011(3)$ Å, $\alpha = 119.03(3)$, $\beta = 91.64(3)$, $\gamma = 108.85(3)°$. The dimeric, centrosymmetrical complex anion $[Au_2(WS_4)_2]^{2-}$ contains bidentate, nearly regular tetrahedral WS_4^{2-} ligands [average WS bond length: 2.136 Å (terminal), 2.243 Å (bridge); SWS bond angles: 105.6–112.9(2)°]. The SAuS linkage is approximately linear [SAuS angle: 167.2(2); AuS bond length: between 2.292(6) and 2.414(6) Å].

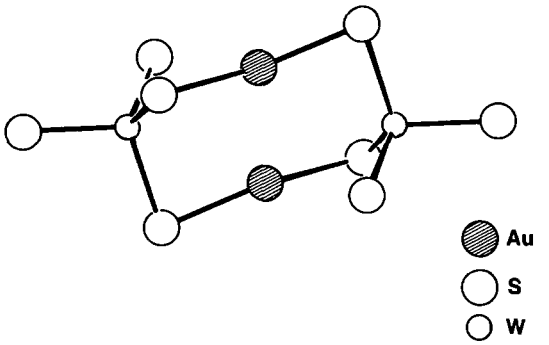


Fig. 1. Structure of the cyclic thioheteroanion $[Au_2(WS_4)_2]^{2-}$.

The heteroanion is disordered in the crystal structure, the Au atoms being distributed over three positions. Therefore, three orientations of identical rings (twisted by nearly 120° with respect to each other) can be distinguished.

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Though the IR spectrum of *(1)* [ν(WS) at 494 (m), 489 (m) and ν(AuS) at 329 (w) cm^{-1}] shows the coordination of WS_4^{2-} as a ligand (with significant differences in comparison to the spectra of transition metal coordination compounds where the metal acts as central atom), the molecular structure cannot be deduced from those data. Useful information has been obtained from the 77 keV ^{197}Au Mössbauer spectrum[3]: the quadrupole splitting and the chemical shift ($QS = 5.58$ mm/s, $IS = 0.86$ mm/s) constitute proof of an almost linear SAuS linkage[4], where the bonding involves only 6s and 6p orbitals of gold(I) and the π-acceptor strength of the ligand WS_4^{2-} from Au is negligible (in contrast to transition metal systems with open d shells).

Experimental

To an aqueous solution (600 ml) of $Na_3[Au(S_2O_3)_2]\cdot 2H_2O$ (0.1 g) and $[(C_6H_5)_4P]Br$ (0.24 g) is quickly added a freshly prepared solution (20 ml H_2O) of $(NH_4)_2WS_4$ (0.1 g). After immediate filtration the precipitate is briefly digested in nitromethane (0.7 ml). The residue is dissolved in dimethylformamide (4 ml). After addition of ethanol (4 ml) dark red crystals of *(1)* slowly precipitate (about 15 h); yield 0.04 g (27%).

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CAS Registry numbers:
(1), 65015-83-0; $Na_3[Au(S_2O_3)_2]$, 12256-50-7; $(NH_4)_2WS_4$, 13862-78-7

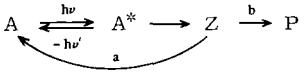
[1] See *E. Diemann, A. Müller*, Coord. Chem. Rev. *10*, 79 (1973); *A. Müller, S. Sarkar*, Angew. Chem. *89*, 748 (1977); Angew. Chem. Int. Ed. Engl. *16*, 705 (1977); references cited therein.
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[3] The spectrum of the powdered sample was measured with a ^{197}Pt source (obtained by thermal neutron capture of ^{196}Pt) at 4.2 K, normal transmission geometry and integrating counting technique (velocity measurement with a Michelson interferometer). See *M. P. A. Viegers, J. M. Trooster*, Nucl. Instrum. Methods *118*, 257 (1974). *IS* relative to ^{197}Au in Pt.
[4] See *P. G. Jones, A. G. Maddock, M. J. Mays, M. M. Muir, A. F. Williams*, J. Chem. Soc. Dalton Trans. *1977*, 1434; *M. P. A. Viegers*, Thesis, University of Nijmegen 1976.

Novel Method for the Detection of Indirectly Identifiable Photochemical Intermediates[**]

By *Gerd Kaupp* and *Heinz-Willi Grüter*[*]

Kinetic, flash spectroscopic, and magnetic (ESR, CIDNP) methods have been used for the detection of short-lived photointermediates[1], but none of these techniques is universally applicable.

In *thermally supported photoreactions* a comparison of the temperature dependence of luminescence and photochemical quantum yield provides mechanistic data. For example, if a singlet photoreaction A→P proceeds in two steps *via* an intermediate Z, its quantum yield can decrease or increase

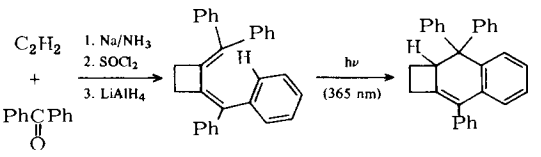


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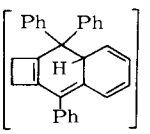
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

with decreasing temperature[2], so long as the formation of Z remains unhindered. The temperature dependence of the fluorescence yield, on the other hand, is independent of the ratio *a/b*. In contrast, direct transitions from A* to P (concerted reactions without Z) necessitate an inverse relationship between quantum yield and fluorescence rate.

The application of these principles can be illustrated quite clearly by the productive intramolecular photoaddition of an aromatic C—H bond to an exocyclic double bond in *(1)*.



(1) *(2)*



(3)

Compound *(1)*[3], which is readily accessible from acetylene and benzophenone, largely avoids α- and β-cleavages[4] after absorption of light. The photolysis leads to 95 % *(2)*, whose structure has been confirmed by ^{1}H-NMR, ^{13}C-NMR, UV, IR, and mass spectra and by elemental analysis[5]. In contrast to the related photoreactions of fulgides[6] no absorption spectrum of a colored intermediate having structure *(3)* can be recorded at temperatures down to −80 °C, and there is still no experimental evidence for corresponding formulations in the isomerizations of overcrowded indan derivatives[7]. Evidence for (or against) an intermediate is therefore urgently required:

Compound *(1)* does not fluoresce at 25 and −80 °C but does so very intensely at −190 and −196 °C [ether/ethanol = 1:2; λ_{max}^{corr} = 460 (sh), 482, 494 (sh), 512 (sh), 527 nm (sh)]. This is fundamentally different from the temperature dependence of the photochemical formation of *(2)*, which proceeds seven times more slowly at −80 °C than at 25 °C (365 nm) and not at all at −190 °C [here also no colored product, but now stability of *(1)*]. Obviously the formation of an intermediate product [presumably *(3)*] from electronically excited *(1)* is unhindered down to −80 °C, but at −190 °C is no longer possible because of a slight energy barrier. The *a/b* ratio [here the ratio of the formation of *(1)* and of *(2)* from *(3)*] is in principle temperature dependent, since it is based on competing thermally activated processes.

The observed kinetic effect is independent of whether the intermediate product does or does not enrich to the UV detection limit under the irradiation conditions (I_0 *ca.* 4×10^{-8} E/s). As a further consequence of the mechanism *via* an intermediate, an influence of the solvent on the *a/b* ratio, *i.e.* on the photochemical quantum yield (cyclohexane: 0.0049, ethyl bromide: 0.0039, benzene: 0.0038, dichloromethane: 0.0027, methanol: 0.0026, acetonitrile: 0.0026), must be expected. The measured (N_2 or O_2, 25 °C, λ = 365 nm)[1a] values, which are very reliable because of the disappearing steady state concentration of *(3)* (in the transparent solvents three isosbestic points between 220 and 300 nm) confirm this prediction and at the same time also the singlet mechanism.

This method of detection of short-lived photointermediates should also be applicable to reactions which can be frozen-in only below 77 K, and still other deactivation processes might be useful instead of fluorescence.

3,3,8-Triphenyl-1,2,2a,3-tetrahydrocyclobuta[b]naphthalene (2):

A solution of 1,2-bis(diphenylmethylene)cyclobutane *(1)* (1.0 g) in benzene (300 ml) is irradiated at 20—25 °C with a mercury high-pressure lamp (Hanau, Q-81) through a glass filter (Wertheimer UVW-55) or a 0.5 M $Cu(NO_3)_2$ solution (1 cm) while being mixed by passage of a stream of N_2. After *ca.* 16 h the UV spectrum of *(1)* (λ_{max} = 357 nm) has all but disappeared. The solvent is removed and the residue crystallized by addition of 50 ml boiling methanol: 950 mg *(2)*, m.p. 180—181 °C.

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CAS Registry numbers:
(1), 24519-15-1; *(2)*, 65138-40-1; acetylene, 74-86-2; benzophenone, 119-61-9

[1] a) *G. Kaupp*, Angew. Chem. *83*, 361 (1971); Angew. Chem. Int. Ed. Engl. *10*, 340 (1971); Justus Liebigs Ann. Chem. *1973*, 844; b) *W. Demtröder*, Top. Curr. Chem. *17*, 1 (1973); *S. Kimel, S. Speiser*, Chem. Rev. *77*, 437 (1977); c) *J. K. S. Wan*, Adv. Photochem. *9*, 1 (1974); d) *H. D. Roth*, Mol. Photochem. *5*, 91 (1973); *B. Blank, A. Henne, G. P. Laroff, H. Fischer*, Pure Appl. Chem. *41*, 475 (1975).

[2] Examples: *G. Kaupp*, Angew. Chem. *88*, 482 (1976); Angew. Chem. Int. Ed. Engl. *15*, 442 (1976); the reactions mentioned are single-quantum processes, since there is a linear (not quadratic) intensity dependence.

[3] *E. V. Dehmlow*, Tetrahedron Lett. *1969*, 4283; and references cited therein.

[4] *G. Kaupp*, Angew. Chem. and Angew. Chem. Int. Ed. Engl., in press.

[5] *(2)* is rigid and has a sterically crowded bond β to the double bond in the central ring. Photolysis (253.7 nm) at 83 K leads to a wine-red, very light-sensitive (546 nm) compound (broad absorption band at λ_{max} = 524 nm), which does not survive on warming to −90 °C and must be regarded as 5-(1-cyclobutenyl)phenylmethylene-6-diphenylmethylene-1,3-cyclohexadiene. Cf. also *U. Widmer, H. Heimgartner, H. Schmid*, Helv. Chim. Acta *58*, 2210 (1975).

[6] *A. Santiago, R. S. Becker*, J. Am. Chem. Soc. *90*, 3654 (1968); *R. J. Hart, H. G. Heller, K. Salisbury*, Chem. Commun. *1968*, 1627.

[7] *H. G. Heller, K. Salisbury*, J. Chem. Soc. *C 1970*, 873.

Selenium Dioxide Insertion into the Iron-Methyl Bond of η^5-$C_5H_5Fe(CO)_2CH_3$[1]

By *Ingo-Peter Lorenz*[*]

SO_2 insertions into transition metal-carbon bonds have long been used for the synthesis of sulfinato complexes[2]. Corresponding insertion reactions of the homologous SeO_2 have so far not been described.

We report here on the first synthesis of a novel seleninato complex[3] by SeO_2 insertion into the iron-methyl bond of η^5-$C_5H_5Fe(CO)_2CH_3$ *(1)*: freshly sublimed SeO_2 completely dissolves in a well stirred solution of *(1)* in benzene, and a precipitate of *(2)* is immediately formed according to

$$\underset{(1)}{\eta^5\text{-}C_5H_5Fe(CO)_2CH_3} + SeO_2 \rightarrow \underset{(2)}{\eta^5\text{-}C_5H_5Fe(CO)_2Se(O)_2CH_3}$$

Some by-products are formed at the same time, including a little $[\eta^5\text{-}C_5H_5Fe(CO)_2]_2$ and large amounts of tris(methaneseleninato-*O,O'*)iron(III), $Fe(O_2SeCH_3)_3$[3b]. *(2)* is a brown,

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finely crystalline solid which is stable in air for a few days, is not sublimable *in vacuo* below 130°C, and in the freshly prepared state is only moderately soluble in CH_2Cl_2 and CH_3OH; it is insoluble in other solvents. The composition and structure of the compound has been confirmed by elemental analysis and mass, ^1H-NMR, and IR spectroscopy.

The monomolecular structure of *(2)* in the dissolved and in the gaseous states follows from the molecular weight (obs. 300, osmometric in CH_2Cl_2) and the mass spectrum, which shows, besides the molecular ion ($m/e = 302$ and 304 in the natural isotopic ratio, 70 eV, 120°C), the successive elimination of the two CO ligands and the CH_3SeO_2 group (with fragmentation) as well as the recombination product $[\eta^5\text{-}C_5H_5Fe(CO)_2]_2$ as the ion of greatest mass. The 60-MHz ^1H-NMR spectrum (CD_3OD) shows two singlets at $\delta = 3.02$ (CH_3) and 5.05 (C_5H_5) in the expected intensity ratio. The chemical shift of the methyl protons excludes an Fe—C bond; the shift of the cyclopentadienyl protons of *(2)* downfield compared to those of the starting compound *(1)* can be explained by the electronegative character of the seleninate group.

In the IR spectrum of *(2)* the two $\nu(C{\equiv}O)$ frequencies (C_s symmetry, A′ + A″) appear as singlets at 2056 and 2009 cm^{-1} (in CH_2Cl_2) and thus—as in the case of the corresponding sulfinato complex[4] (as doublets)—lie about 50 cm^{-1} higher than in the spectrum of *(1)*; they indicate substantial π-acceptor ability of the seleninate ligands. Since no absorption occurs in the acyl-CO region (1700—1580 cm^{-1}) a reaction analogous to "CO-insertion"[5] can be ruled out. This is confirmed by $\nu(SeC)$ and $\nu(SeO_2)$ vibrations: As in the case of other alkaneseleninates $\nu(SeC)$ is observed at 570 cm^{-1} (in KBr); the position and frequency of $\nu_{as}(SeO_2)$ and $\nu_s(SeO_2)$ of compound *(2)* [859 (s) and 728 (s) cm^{-1}, respectively; solid/KBr] are consistent with coordination of the $RSeO_2^-$ group *via* selenium (seleninato-*Se* type)[3]. Hence, *(2)* can be regarded as a stable organometallic derivative of the highly reactive selenones. The reverse reaction, *i.e.* cleavage of SeO_2 from *(2)*, has not been observed.

(2) can be synthesized in the form of red-brown finely crystalline needles (m.p. 140°C) also by reaction of $\eta^5\text{-}C_5H_5Fe(CO)_2Cl$ with sodium methaneseleninate in dichloromethane or methanol[3b]:

$$\eta^5\text{-}C_5H_5Fe(CO)_2Cl + CH_3SeO_2Na \rightarrow (2) + NaCl$$

Experimental[6]

A suspension of freshly sublimed SeO_2 (2.22 g, 20 mmol) in a solution of *(1)* (3.88 g, 20 mmol) in benzene (50 ml) is stirred for 5 h at 50°C, filtered, and the unreacted *(1)* and $[\eta^5\text{-}C_5H_5Fe(CO)_2]_2$ washed with benzene. After brief drying the residue is extracted for *ca.* 6 h with 70 ml boiling dichloromethane using an extraction frit. The resulting solution is concentrated by evaporation and cooled, whereupon a brown crystalline product separates out. Filtration, washing with petroleum ether, and vacuum drying affords 720 mg (12%) *(2)*, m.p. 138—139°C. The residue from the extraction contains exclusively $Fe(O_2SeCH_3)_3$[3b].

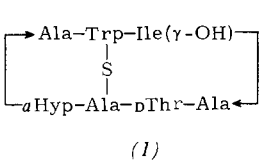
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German version: Angew. Chem. 90, 60 (1978)

[1] Coordination Chemistry of Ambivalent Ligands, Part 9.—Part 8: *I. P. Lorenz, J. K. Thekumparampil*, Z. Naturforsch. *B*, in press.
[2] *G. Vitzthum, E. Lindner*, Angew. Chem. *83*, 315 (1971); Angew. Chem. Int. Ed. Engl. *10*, 315 (1971); *A. Wojcicki*, Adv. Organomet. Chem. *12*, 32 (1974); and references cited therein.
[3] a) Cf. *C. Preti, G. Tosi*, Spectrochim. Acta *A 31*, 1139 (1975); references cited therein; b) *I.-P. Lorenz*, unpublished.
[4] *J. P. Bibler, A. Wojcicki*, J. Am. Chem. Soc. *88*, 4862 (1966).
[5] *F. Calderazzo*, Angew. Chem. *89*, 305 (1977); Angew. Chem. Int. Ed. Engl. *16*, 299 (1977).
[6] In the meantime $\eta^5\text{-}C_5H_5Mo(CO)_3Se(O)_2CH_3$ has also been prepared *via* an analogous route [3b].

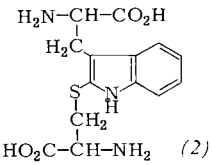
L,L-3,6-[Methanothio(2,3-indolo)methano]piperazine-2,5-dione, the Smallest Phallotoxin Model

By *Theodor Wieland, Christian Birr*, and *Giancarlo Zanotti*[*]

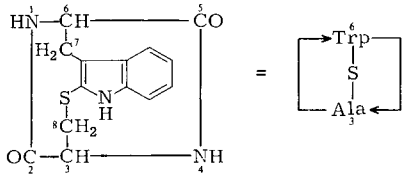
The phallotoxins [*e.g.* phalloin *(1)*], bicyclic heptapeptides from the green deathcap toadstool *(Amanita phalloides)*[1], contain a thioether bridge linking the mercapto group of a former cysteine with position 2 of a tryptophan side chain as a characteristic structural unit. The double amino acid *S*-(2-tryptophanyl)cysteine *(2)* was called tryptathionine[2].



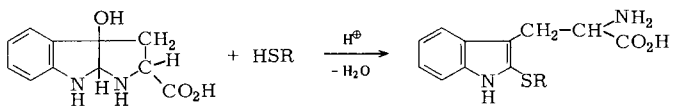
(1)



(2)

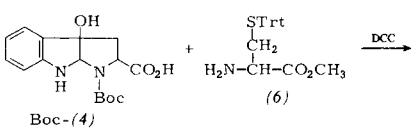


(3)

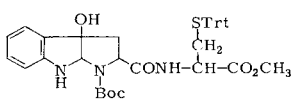


(4) *(5)*

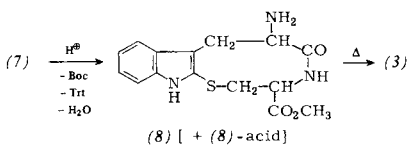
The intramolecular double cyclic peptide of *(2)*, a piperazinedione *(3)*, is the first member of an interesting series



Boc-*(4)* *(6)*



(7)



(8) [+ *(8)*-acid]

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of phallotoxins. Our synthesis of this "miniphallotoxin" made use of a publication by *Savige* and *Fontana*[3], according to which 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid *(4)* (designated here as Hpi), obtained from L-tryptophan by oxidation with peracetic acid[4], reacts with thiols in the presence of acids including cysteine[3] to give good yields of 2^{ind}-thioethers *(5)* of tryptophan. Since we wished to use this approach for synthesizing bicyclic peptides of type *(1)* it was be to examined whether with the smallest peptide model *(7)* the thioether formation induced by protonation also leads to the cyclic product *(8)*.

In order to use the diastereomeric "proline derivative" *(4)*[4] as the acyl component of a dipeptide synthesis with L(*S*-trityl)-cysteine methyl ester *(6)* it was protected at the pyrrolidine nitrogen by *tert*-butoxycarbonylation and coupled in this form (as Boc-*(4)*) to *(6)* with the aid of dicyclohexylcarbodiimide (DCC). The *S*- and *N*-protecting groups were removed from the dipeptide ester *(7)* by 50% trifluoroacetic acid, which led to simultaneous formation of cyclic thioether *(8)*. However, since the methyl ester *(8)* is partly hydrolyzed (to the *(8)*-acid), this component must subsequently be transformed back into *(8)* (with intermediate Boc protection of the primary amino function). On heating in *sec*-butyl alcohol/toluene the nine-membered monocyclic compound *(8)* gives the bicyclic piperazinedione *(3)*. This, the simplest phallotoxin analog was identified by elemental analysis and UV and mass spectrometry; it is nontoxic and shows no affinity for F-actin[5].

Experimental

N^{pyr}-Boc-Hpi [Boc-*(4)*]: A suspension of crystalline Hpi[4] (11.5 g, 0.053 mol) in dioxane/water (1:1, 50 ml) is stirred with Boc-azide (21.45 g, 0.15 mol) at room temperature for 3 h at pH 9.5 to 10 (0.5 N NaOH, pH stat). After removal of dioxane, the aqueous solution is washed once with ether and, after acidification to pH 3 with citric acid, several times with ethyl acetate. After washing twice with water and drying over Na_2SO_4 the solution is evaporated down *in vacuo* and the residue recrystallized from ethyl acetate: yield 14.0 g (81%); m.p. 180°C, $[\alpha]_D = +170°$ ($c = 1$, methanol).

Boc-Hpi-Cys(Trt)OMe *(7)*: A solution of Boc-*(4)* (5.8 g, 19.1 mmol) in ethyl acetate (120 ml) is stirred for 1 h with a solution of *(6)*[6] (7.2 g, 19.1 mmol) in dichloromethane (400 ml) at 0°C with admixture of dicyclohexylcarbodiimide (3.93 g, 19.1 mmol) in dioxane (50 ml), and then for 4 h at 20°C. The dicyclohexylurea is filtered off and the filtrate washed with 50% citric acid (2×), 0.5 N hydrogencarbonate (2×), and water (2×), and then dried over Na_2SO_4. The noncrystalline evaporation residue amounts to 13.4 g (≈100%). A sample purified by preparative thin layer chromatography (ether/light petroleum (65°C), 8:2) shows $[\alpha]_D = +71°$ ($c = 0.6$, methanol).

Cyclosulfide *(8)* and *(8)*-acid: A solution of *(7)* (13 g, 19 mmol) in 50% trifluoroacetic acid (260 ml) is maintained at 20°C for 48 h, filtered, and evaporated *in vacuo*. The residue is digested several times with ether and chromatographed with methanol on Sephadex LH-20. The first UV absorbing substance to appear is *(8)* (260 mg), followed directly by *(8)*-acid (760 mg), $\varepsilon_{290} = 10370$ (in methanol). In order to esterify the acid a 500-mg sample (1.63 mmol) in dioxane/water (1:1) is converted, in an autotitrator at pH 10 as described above, into the Boc derivative of the primary amino group with Boc-azide (466 mg, 3.26 mmol); it precipitates on acidification during work-up in the same way as for *(4)*. The precipitate is filtered off, washed with water, and dried in a desiccator. A 330-mg sample of Boc-*(8)*-acid is methylated with diazomethane in ether, and the methyl ester obtained on evaporation is transformed into *(8)* on standing in trifluoroacetic acid for 20 min. 250 mg is isolated (100%).

Piperazinedione *(3)*: A solution of *(8)* (250 mg) in a 2:1 mixture of *sec*-butyl alcohol and toluene is heated under reflux for 3 h. The crystals precipitated on cooling (84 mg) are filtered off under suction, washed with methanol, and recrystallized from the 2:1 solvent mixture: 36 mg of *(3)*, dec. >290°C. $[\alpha]_D = +429°$ ($c = 0.1$, methanol). MS (Dr. *H. J. Förster*, Ingelheim): $m/e = 287$. $\varepsilon_{290} = 10470$ (methanol). The ^{1}H-NMR spectrum shows all the expected proton signals; in the ^{13}C-NMR spectrum the signals (TMS as standard) of C-3 or C-6 appear at 53.38 or 54.07, of C-2 or C-5 at 166.85 or 170.91, of C-7 at 44.39, and of C-8 at 28.11 (Dr. *K. H. Pook*, *W. Pryss*, Ingelheim).

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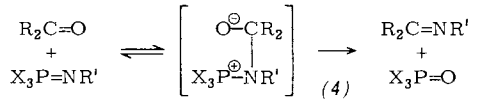
CAS Registry numbers:
(2), 61348-31-0; *(3)*, 65138-59-2; *(4)*, 35169-97-2; Boc-*(4)*, 65121-41-7; *(6)* 58885-35-1; *(7)*, 65121-42-8; *(8)*, 65121-44-0; *(8)*-acid, 65121-45-1; Boc-*(8)*-acid, 65121-47-3; Boc-*(8)*, 65121-50-8

[1] *Th. Wieland, O. Wieland* in *S. Kadis, A. Ciegler, S. J. Ajl:* Microbial Toxins, Vol. 8. Academic Press, New York 1972, p. 249.
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[3] *W. E. Savige, A. Fontana*, J. Chem. Soc. Chem. Commun. *1976*, 600.
[4] *W. E. Savige*, Aust. J. Chem. *1975*, 3375.
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[6] *L. Zervas, J. Photaki*, J. Am. Chem. Soc. *84*, 3887 (1962).

Stable [2+2]-Cycloadducts of Ketones with Phosphazenes Having Five-Membered Rings[1]

By *Alfred Schmidpeter* and *Thomas von Criegern*[*]

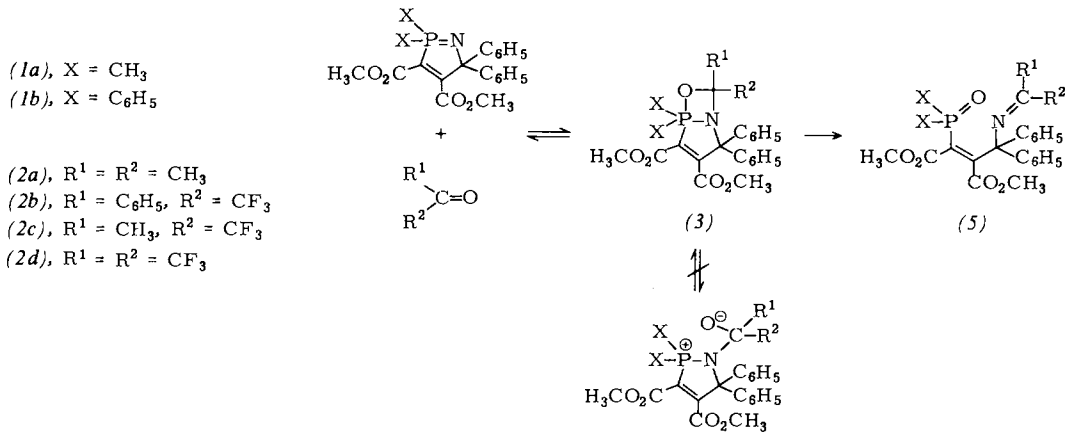
On the basis of kinetic studies a betaine intermediate has recently been proposed to occur in the reaction of λ^5-phosphazenes (phosphane imides) with aldehydes or ketones discovered by *Staudinger et al.*[2]; the reaction products are assumed to form from it *via* a four-membered ring containing pentacovalent phosphorus[3]:



However, it was pointed out that, in contrast to the situation in the Wittig reaction, there is still no direct experimental evidence for an intermediate and that mechanistic alternatives therefore cannot be unequivocally ruled out[3].

In the reaction of five-membered ring phosphazenes such as 1,2λ^5-azaphospholes *(1)*[4] with ketones *(2)* we have now isolated the crystalline [2+2]-cycloadducts *(3)*[5]. Their bicyclic structure follows from the characteristic upfield shift of pentacoordinated phosphorus observed in the ^{31}P-NMR spectrum (Table 1) and from the diastereotopism of X = CH_3

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observed for *(3b)* and *(3c)* ($R^1 \neq R^2$) in the ^{1}H-NMR spectrum. $\delta(^{31}P)$ shows a clear-cut and regular progression to lower field with each CF_3 group, indicating increasing polarity of the PO bond on going from *(3a)* to *(3d)* and from *(3e)* to *(3h)*. However, an equilibrium contribution of the betaine form *(4)* [$\delta(^{31}P)$ value predicted $\approx +70$] can be ruled out since the ^{31}P shift of the adduct hardly changes with solvent polarity (Table 1).

Table 1. ^{31}P-NMR shift in $CDCl_3$ (or Me_2SO) and proportion Q of the cycloadducts *(3)* dissociated (0.7 M $CDCl_3$ solution).

	X	R^1	R^2	$\delta(^{31}P)$	Q [%] at T [°C] = −20	0	20	40	60
(3a)	CH_3	CH_3	CH_3	−55.4		34	53	65	80
(3b)	CH_3	C_6H_5	CF_3	−46.6				10	18
(3c)	CH_3	CH_3	CF_3	−46.6 (−44.6)				—	
(3d)	CH_3	CF_3	CF_3	−35.1 (−34.0)				—	
(3e)	C_6H_5	CH_3	CH_3	−49.3	76	92			
(3f)	C_6H_5	C_6H_5	CF_3	−43.2	42	59	67	74	
(3g)	C_6H_5	CH_3	CF_3	−41.2				11	19
(3h)	C_6H_5	CF_3	CF_3	−34.9				—	

Some of the cycloadducts decompose to their components in solution; their ^{1}H-, ^{19}F-, and ^{31}P-NMR spectra show signals of *(1)* and *(2)* in addition to those of *(3)*. Dissociation is promoted by dilution and by higher temperatures (Table 1). The positions of the equilibria reveal that the stability of the cycloadducts towards reversion *(3)* is determined mainly by the acceptor strength of the ketone *(2a)* < *(2b)* < *(2c)* < *(2d)* and by the donor strength of the phosphazene *(1a)* > *(1b)*. The adduct of lowest stability *(3e)* dissociates completely at room temperature in 0.7 M $CDCl_3$ solution. It also quantitatively regenerates *(1b)* on dry warming *in vacuo*, in the same way as *(3a)* regenerates *(1a)*.

On heating solutions of the other cycloadducts *(3)* to >60 °C, reversible dissociation is accompanied by slow irreversible decomposition. The alternative [2+2]-cleavage of the oxazaphosphete ring gives the ketimine-phosphane oxides *(5)*, in keeping with *Staudinger*'s results[2]. Unlike ketones, aldehydes such as *(2)*, $R^1 = H$, $R^2 = CCl_3$, p-$C_6H_4NO_2$, C_6F_5 immediately react with *(1)* to give the ring-opened product *(5)*; no intermediate *(3)* can be detected.

From our results a four-membered ring intermediate rather than a betaine intermediate appears likely in general for the carbonyl/iminophosphorane reaction, as in the Wittig reaction[6]. It can be isolated in the exceptional case of *(3)* owing to the stabilizing effect of incorporation of σ^5-phosphorus as bridgehead[7].

7-Oxa-5-aza-1-phosphabicyclo[3.2.0]hept-2-enes (3)

An excess of the ketone *(2)* is added to the yellow concentrated solution of *(1)* in $CHCl_3$, which is usually decolorized. On addition of *n*-pentane the colorless cycloadduct *(3)* is precipitated and can be recrystallized from $CHCl_3$/*n*-pentane.

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(1a), 33536-07-1; *(1b)*, 65138-44-5; *(2a)*, 67-64-1; *(2b)*, 434-45-7; *(2c)*, 421-50-1; *(2d)*, 684-16-2; *(2)* ($R' = H$, $R^2 = CCl_3$), 75-87-6; *(2)* ($R' = H$, $R^2 = pC_6H_4NO_2$), 555-16-8; *(2)* ($R' = H$, $R^2 = C_6F_5$), 653-37-2; *(3a)*, 65138-45-6; *(3b)*, 65138-46-7; *(3c)*, 65138-47-8; *(3d)*, 65138-48-9; *(3e)*, 65138-49-0; *(3f)*, 65138-50-3; *(3g)*, 65138-51-4; *(3h)*, 65138-52-5; *(5)* ($X = CH_3$; $R' = H$, $R^2 = CCl_3$), 65138-53-6; *(5)* ($X = CH_3$; $R' = H$; $R^2 = pC_6H_4NO_2$), 65138-54-7; *(5)* ($X = CH_3$; $R' = H$; $R^2 = C_6F_5$), 65138-55-8; *(5)* ($X = Ph$; $R' = H$, $R^2 = CCl_3$), 65138-56-9; *(5)* ($X = Ph$; $R' = H$; $R^2 = pC_6H_4NO_2$), 65138-57-0; *(5)* ($X = Ph$; $R' = H$; $R^2 = C_6F_5$), 65138-58-1

[1] Part 28 of Four- and Five-Membered Phosphorus Heterocycles, also Part 60 of Phosphazenes. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.— Parts 27 and 59, respectively: *R. Mathis, T. Bouisson, M. Bon, A. Schmidpeter, J. Luber, M. Volz*, Spectrochim. Acta, in press, and *A. Schmidpeter, J. Luber, H. Tautz*, Angew. Chem. *89*, 554 (1977); Angew. Chem. Int. Ed. Engl. *16*, 546 (1977).
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Synthesis of *cyclo*-Heptasulfur, S_7, from S_8[1]

By *Ralf Steudel* and *Hans-Joachim Mäusle*[*]

On melting, *cyclo*-octasulfur is transformed into a mixture of S_8, S_7, S_6, and S_μ (polymeric sulfur insoluble in CS_2)[2];

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at the equilibrium melting point (115.2 °C) the concentration of S_7 is *ca.* 4 % w/w and at the polymerization temperature (159 °C) *ca.* 8 %[3]. The formation of S_7 and S_6 most likely proceeds *via* S_μ, which arises from S_8 by homolytic ring-opening and copolymerization of the chain with *cyclo*-S_8[4] and from which, conversely, small cyclic molecules can be split off. We have now found that S_7 can be isolated in pure form with little effort from quenched sulfur melts by fractional extraction and crystallization exploiting the tendency of S_7 to form supersaturated solutions in CS_2. Precipitation can be achieved by inoculation with S_7 or addition of finely ground glass. The S_7 thus obtained shows no contamination by S_8 or S_6 in the Raman spectrum and is identical with that obtained as condensation product from $(C_5H_5)_2TiS_5$ and S_2Cl_2[5]. The yield is *ca.* 10 % of the S_7 present in equilibrium in liquid sulfur at 159 °C; most of the unconverted sulfur can be processed again for the synthesis of S_7. No exacting measures are required regarding the purity of the sulfur or the solvent.

At an annual world production of *ca.* 30×10^6 t of liquid sulfur, containing *ca.* 2×10^6 t S_7 in equilibrium, these results would justify a more detailed investigation of the chemical properties of *cyclo*-heptasulfur.

Experimental

100 g sulfur is heated in a 250 ml round-bottom flask at 200 °C for 30 min and then *slowly* cooled to 159 °C. As soon as the melt has become less viscous it is allowed to flow in as thin a stream as possible into liquid nitrogen. The liquid nitrogen is removed very carefully by decantation from the bright yellow powder, which is then extracted at room temperature with purified CS_2 (70 ml) for 1 h with vigorous stirring. The intensely yellow solution is filtered and stored for 20 h at −78 °C, whereupon S_8 crystallizes out. The solution is then decanted, which must be carried out as quickly as possible so as to prevent any S_8 being redissolved on warming. The solution is stirred for 2 h in a 100-ml round-bottom flask at −78 °C together with finely-ground glass (3 spatulasful) until precipitation of finely crystalline sulfur. After settling the precipitate is sucked as dry as possible using an immersion filter frit (D3 or D4), and then rapidly extracted (3 × 10 ml) with analytically pure toluene at 25 °C, the solution being decanted off each time from the orange red residue. On cooling the combined extracts, finely crystalline S_7 precipitates out. The mother liquor is carefully decanted off or sucked off as above; the product is dissolved in CS_2 (5 ml), crystallized out again at −78 °C, and isolated by rapid suction at a glass-frit. Depending on the melting point the product is again recrystallized once or twice from CS_2. Yield: 0.6–0.8 g needle-shaped or lance-shaped, intensely yellow crystals (m.p. 38–39 °C); solubility at −78 °C: 1.7 g/100 g CS_2.

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X-Ray Structure Analysis of *cyclo*-Decasulfur, S_{10}[1]

By *Richard Reinhardt, Ralf Steudel*, and *Fritz Schuster*[*]

cyclo-Decasulfur is obtainable in the form of thermally unstable, light-sensitive, yellow crystals as product of the reaction of $(C_5H_5)_2TiS_5$ with SO_2Cl_2, and has been characterized by molecular weight determination[2], mass spectra[3], and vibrational spectra[4]. Controlled decomposition of *cyclo*-polysulfur oxides such as S_6O_2 and S_7O also leads to pure crystalline S_{10}[5]; to elucidate the mechanism of formation of S_{10} we have carried out a single-crystal X-ray structural analysis.

The space group and approximate lattice constants were determined from deJong-Bouman and precession photographs at *ca.* −110 °C. The results showed the monoclinic space group C2/c with an unusually small angle of 37° for the normal setting, but with an angle of 110° after transformation into I2/n. Refinement of 24 Bragg angles according to the method of least squares afforded the cell constants in I2/n: $a = 824.0(4)$, $b = 1027.5(9)$, $c = 1277.6(9)$ pm, $\beta = 110.59(2)°$, $Z = 4$, $d_{calc} = 2.103\ g \cdot cm^{-3}$ (−110 °C). 961 independent reflections up to $\theta = 25°$ were measured on an automatic single-crystal diffractometer using $Mo_{K\alpha}$ radiation and corrected in the usual way; 19 reflections were classified as unobserved ($I \leq 2\sigma$). A meaningful prediction of the structure was not achievable with direct methods and the interpretation of a Patterson synthesis did not appear promising. However, on the basis of spectroscopic measurements and symmetry considerations[4] the possible arrangements of the atoms were so limited that the phase problem could be solved by trial and error methods and the structure refined with anisotropic temperature factors to $R = 0.039$. An absorption correction ($\mu = 20.07\ cm^{-1}$) was not carried out.

The four S_{10} molecules in the unit cell occupy C_2 symmetry positions, but to a good approximation have the very rare point group symmetry D_2 (three orthogonal twofold axes of rotation as the only symmetry elements). Six atoms lie in a plane (maximum deviation from the least squares plane 1.5 pm) and two atoms are situated above and two below the plane (see Fig. 1). This conformation, which hitherto has not been observed in sulfur chemistry, does not correspond to the predicted D_{5d} symmetry[6]. The arithmetical mean bond lengths (205.6 pm) and valence angles (106.2°) closely correspond to the values observed in S_{12} (205.3 pm, 106.6°[7]); formally, S_{10} can be composed of two identical S_5 units, obtain-

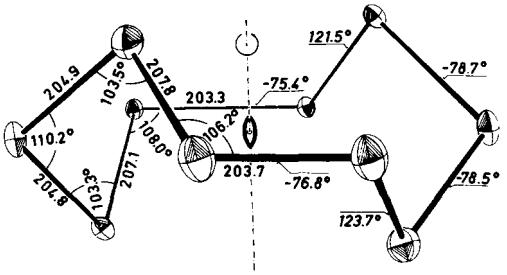


Fig. 1. Molecular structure, bond lengths [pm], valence angles, and torsion angles of S_{10}. The maximum standard deviation of the bond lengths is 0.4 pm, that of the angles 0.2°. The crystallographic two-fold symmetry axis is shown. The distance between the two horizontal bonds is 541 pm.

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able from the S_{12} molecule (left and right halves of the molecule in Fig. 1).

Although no unusually long or short bonds are present, an alternation of bond lengths symmetric to one of the C_2 axes is clearly recognizable. This can be interpreted in terms of the alternating torsion angles which have the value 123 ± 2 or $-77\pm2°$, the greater value leading to a weakening of the SS bonds which then gives rise to a slight shortening of the neighboring bonds owing to strong bond-bond interaction[7]. The lower thermal stability of S_{10} compared to that of S_8 and S_{12} can be attributed to the four large torsion angles of *ca.* 123°, which exceed the previously observed values in sulfur rings by more than 20°. This results in a stronger electron pair repulsion between neighboring atoms and thus a decrease in bond energy[7]. The smallest intermolecular distance between nuclei is 323 pm.

Hence the structures of the sulfur homocycles S_n with $n=6$, 7, 8, 10, 12, 18, and 20 are now known.

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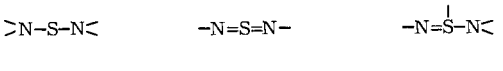
CAS Registry number:
S_{10}, 12597-15-8

[1] Part 54 of Sulfur Compounds. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 53: *R. Steudel, H.-J. Mäusle*, Angew. Chem. *90*, 54 (1978); Angew. Chem. Int. Ed. Engl. *17*, 56 (1978).
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An Alkylsulfur Imide Amide (Methanesulfinamidine)—Relation between Coordination Number and Bond Length[**]

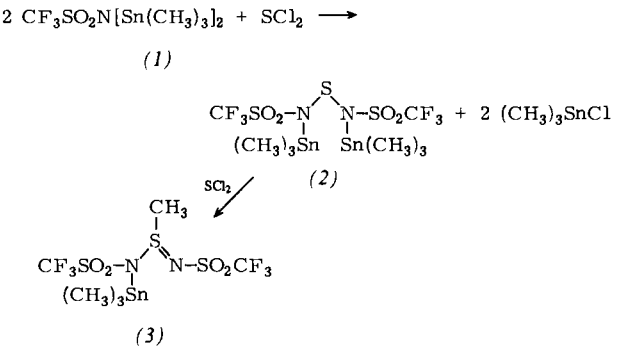
By *Herbert W. Roesky, Manfred Diehl, Hartmut Fuess*, and *Jan Willem Bats*[*]

Reaction of sulfur dichloride with nitrogen-containing organometallic compounds is a known method for the synthesis of sulfur diamides *(A)* and sulfur diimides *(B)*[1]. To our knowledge, however, no sulfur derivatives of type *(C)* have yet been prepared in this way[1b].



(A) *(B)* *(C)*

We have now found that *N,N*-bis(trimethylstannyl)trifluoromethanesulfonamide[2] *(1)* reacts with sulfur dichloride in the molar ratio 2:1 to give the sulfur diamide *(2)*. On treatment with an additional amount of SCl_2 compound *(2)* affords the methylsulfur imide amide *(3)*. Alkylation of sulfur with cleavage of a R_3Sn group was observed for the first time in this reaction.



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

The white crystalline product *(3)* could not be unequivocally characterized by elemental analysis, mass spectrum, ^1H- and ^{19}F-NMR spectra (the structure of a *N*-methyl derivative of type *(A)* could not be ruled out).

In addition to proving the structure, X-ray analysis provided further information. On the one hand, conventional formulation with alternate single and double bonds, as shown for *(3)*, is unsuitable for describing the actual bonding. A correlation apparently exists between the bond lengths and the coordination numbers (CN) of the participating atoms (cf. Fig. 1).

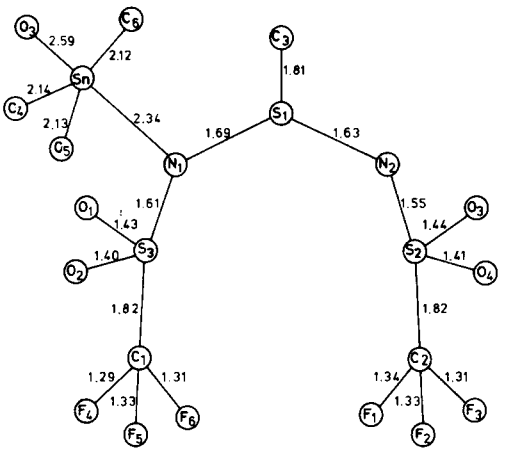


Fig. 1. Molecular structure and numbering of the atoms of *(3)*; bond lengths in Å.

In the case of the shortest SN bond (S2—N2: 155 pm) sulfur has coordination 4 and nitrogen coordination 2. An increase in CN of the atom N1 leads to a lengthening of the S3—N1 distance to 161 pm. A similar effect is observed for the sulfur atom S1 having CN 3. S1—N2 is shorter than S1—N1. According to structural studies performed so far on sulfilimines and sulfamates[3] this observation could be of general validity for sulfur having coordination numbers 4 and 3, leading to the following series of increasing bond lengths:

$$S(CN=4)—N(CN=2) < S(CN=4)—N(CN=3) \approx S(CN=3)—N(CN=2) < S(CN=3)—N(CN=3)$$

On the other hand, the tin atom is in a trigonal-bipyramidal configuration[4] in the crystal, with the three methyl groups,

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the N1 atom, and the O3 atom of an adjacent molecule as nearest neighbors[5].

Experimental

A solution of SCl_2 (1.03 g, 0.01 mol) in CH_2Cl_2 (20 ml) is slowly added dropwise to a stirred suspension of *(1)* (4.77 g, 0.01 mol) in CH_2Cl_2 (30 ml). The red color of SCl_2 disappears, and a clear solution is formed. Compound *(2)* is precipitated as intermediate, and is consumed on further addition of SCl_2. A clear solution is formed once again. On completion of the reaction (*ca.* 3 h) compound *(3)* precipitates; recrystallization from CH_2Cl_2 gives colorless needles, m.p. 132—134 °C. After removal of solvent and sublimation of $(CH_3)_3SnCl$ and $(CH_3)_2SnCl_2$ in an oil-pump vacuum at 40 °C most of the product is obtained as residue; yield 0.5 g.—IR (Nujol, cm^{-1}): 1380 s, 1340 s, 1335 m, 1242 s, 1235 s, 1225 s, 1216 s, 1205 s, 1194 s, 1152 s, 1038 m, 1005 w, 981 m, 917 s, 795 m, 770 m, 767 w, 738 w.—MS (70 eV): *m/e* (rel. int.) = 506 M^+ (1), 491 $M^+ - CH_3$ (59), 165 $(CH_3)_3Sn$ (100).—^{19}F-NMR: $\delta = -77.8$ (s).—^{1}H-NMR: $\delta(CH_3)_3Sn = -0.96$ (s), $\delta(CH_3) = -2.9$ (s).

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(1), 65149-87-3; *(2)*, 65149-88-4; *(3)*, 65167-96-6; SCl_2, 10545-99-0

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The First Reversible Thermal Dissociation of Distannanes, $R_3Sn—SnR_3$

By *Hans U. Buschhaus* and *Wilhelm P. Neumann*[*]

Hexaalkyldistannanes have hitherto been considered as thermally stable up to at least 170 °C[1] or even 235 °C[2]. At higher temperatures irreversible formation of alkyl radicals and polymers, and deposition of tin were observed. As with highly substituted ethanes and their reversible dissociation to alkyl[3] or ketyl radicals[4], the frontstrain or backstrain of bulky residues should also weaken the Sn—Sn bond to such an extent that reversible thermal dissociation may occur. We have now been able to observe this effect in the case of the aryl derivatives *(1)*:

$$\underset{(1)}{R_3Sn—SnR_3} \overset{\Delta}{\rightleftharpoons} \underset{(2)}{2\,R_3Sn\cdot}$$

(a): R = 2,4,6-trimethylphenyl
(b): R = 2,4,6-triethylphenyl

Equal ESR singlets begin to appear in solutions of *(1a)* at 180 °C, and even at 100 °C in solutions of *(1b)*. They disappear instantaneously upon cooling ($g = 2.0075$, line width 5 G). The more bulky ethyl group in *(1b)* is seen to have a considerable influence. ESR intensity measurements gave the dissociation energies $D_{Sn—Sn} = 190 \pm 8$ kJ/mol for *(1a)*, and only 125 ± 5 kJ/mol for *(1b)*, which is considerably less than for $Me_3Sn—SnMe_3$ (210—240 kJ/mol)[5]:

We have prepared the previously unknown distannanes *(1)* by a novel procedure:

$$2\,R_3SnH + NC—CMe_2—N{=}N—CMe_2—CN \overset{\Delta}{\rightleftharpoons} \underset{(3)}{} N_2 + 2\,HCMe_2—CN + \underset{}{(1)}$$

During this reaction, carried out in nonane at 100 °C, the ESR signals of the stannyl radicals *(2)* appear.

Thus, two further transient radicals $R_3Sn\cdot$ have become accessible to measurement in solution, in addition to the tris-(2-phenyl-2-methylpropyl)stannyl radical which was recently subjected to detailed study as an example of this species[6].

Procedure

Preparation of *(1a)*: *(3a)*[7] (1.5 g, 3.1 mmol) is dissolved in anhydrous toluene (50 ml) in an argon atmosphere. Azoisobutyronitrile (0.37 g, 2.2 mmol) is then added, and the mixture is stirred for 8 h at 60 °C. A colorless solid is deposited, which is filtered off with exclusion of air, washed twice with hot toluene, and dried *in vacuo*. Yield: 1.3 g (87 %) of *(1a)*, colorless crystals, dec. > 300 °C, identified by CH analysis, IR, mass spectrometry, very sparingly soluble in the usual solvents, sparingly soluble in phenanthrene or 1-methylnaphthalene.

(1b) is prepared similarly from *(3b)* (5.0 g, 8.3 mmol), obtained by a procedure resembling that for *(3a)*, in nonane (50 ml) and azoisobutyronitrile (1.40 g, 8.3 mmol). After centrifugation and recrystallization from nonane, colorless needles are isolated, dec. > 300 °C, soluble in hot nonane and 1-methylnaphthalene, identified by CH analysis, IR, and mass spectrometry.

Dissociation experiments: In an ESR tube, *(1a)* (about 50 mg) is suspended in 1-methylnaphthalene (1 ml) or melted in phenanthrene (3 g) under argon, or *(1b)* (50 mg) is suspended in 1-methylnaphthalene (1 ml) or nonane (1 ml), and heated to the desired temperature in a Varian E6 X-band ESR spectrometer. Intensity measurements are performed on *(2a)* in the 180—230 °C range (at higher temperatures *(1a)* becomes red and decomposes irreversibly), and on *(2b)* in the 100—160 °C range. The intensities of the signals depend on the applied microwave energy. UV irradiation of *(1a)* and *(1b)* yields *(2a)* and *(2b)*, respectively, even at lower temperatures.

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Bombykal, a Second Pheromone Component of the Silkworm Moth *Bombyx mori L.*

By *Gerhard Kasang, Karl Ernst Kaissling, Otto Vostrowsky,* and *Hans Jürgen Bestmann*[*]

Dedicated to Professor Adolf Butenandt on the occasion of his 75th birthday

In 1959 *Butenandt et al.* reported the isolation and elucidation of the structure of the first insect sex attractant[1]. The compound concerned was (*E*)-10,(*Z*)-12-hexadecadien-1-ol (bombykol), which is secreted from the abdominal glands (sacculi laterales) of the female silkworm moth *Bombyx mori L.* and serves as an attractant only to the male members of the same species. It has hitherto been assumed that bombykol was the only pheromone that played a role in the chemical communication system between the different sexes of the species *Bombyx mori*[2].

Electrophysiological assay of single cells of the olfactory hairs of the male animals showed, however, that only one of the two morphologically different receptor cells[3] was responsive to bombykol, whereas the female's scent excited both cells[4]. This pointed to the presence of a second pheromone component. It was then found that the cell type not excited by bombykol was responsive[4] to (*E*)-10,(*Z*)-12-hexadecadien-1-al (bombykal)[5], a compound recently synthesized in our laboratories. This finding prompted us to search for signs of the presence of bombykal in the glands of the female animal of *Bombyx mori*[6]. We have now succeeded in demonstrating the presence of bombykal in extracts from the abdominal glands of female silk worm moths which were bred in Taiwan and Italy.

The abdominal tips excised from 460 freshly emerged female silkworm moths were together extracted with benzene. The concentrated extract was purified and separated by preparative thin-layer chromatography on silica gel. The zones corresponding to bombykal and bombykol ($R_f = 0.53$ and 0.29, hexane/ethyl methyl ketone = 80:20) were removed[7] and eluted with chloroform/ethanol (99:1). The fractions thus obtained were evaporated to dryness, dissolved in heptane (30 µl), and gas chromatographically analyzed (4 m stainless steel column $^1/_8''$ ID, 3% SE-30 on chromosorb W-AW-DMCS 80/100 mesh, 200°C, isothermal). The results are shown in Table 1.

Table 1. Content of bombykal and bombykol[8] in the extract from 460 abdominal tips excised from female silkworm moths[9].

Compound	Retention time [min]	Total amount [µg]	Content per gland [ng]	Proportion [%]
Bombykal	5.6	7	15.2	7.2
Bombykol	6.8	90	195.7	92.8

The retention times of the natural bombykal and bombykol were identical with those of the synthetic compounds[5]. The GC analyses of the two fractions were repeated on a 50 m thin-film glass capillary (0.32 mm ID, OV 101) coupled to a mass spectrometer[10] (70 eV, EI spectrum, 2.5 s/scan). The retention times of natural and synthetic bombykal and bombykol were once again identical (co-chromatography), being 19.90 and 22.30 min, respectively (splitless injection, 5 min 25°C, 80 to 220°C, 8°/min). The mass spectrum of the fraction with $t_R = 19.90$ min was identical with the spectrum of synthetic bombykal [*m/e* = 236 (M^+, 6%), 235 ($M^+ - H$, 2%), 192 ($M^+ - CH_3CHO$, 0.9%), 67 (100%) and 44 (CH_3CHO^+, 30%)].

The fact that bombykal is present in the abdominal glands of the female *Bombyx mori* and that the antennae of the male have specific and highly-sensitive receptor cells for this compound proves that bombykal is a second pheromone component of the silkworm moth. At the same time it shows that also *Bombyx mori*, the classical "pet" of pheromone research[1, 11], uses a multicomponent system for communication between the sexes, as has been found to be the case for numerous other species of Lepidoptera[12]. The ratio of the components of such a pheromone complex is decisive for its mode of action and species specificity[13].

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CAS Registry number:
Bombykal, 63024-98-6

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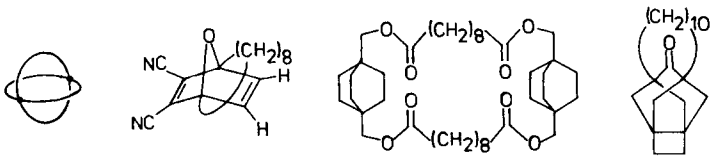
[1] *A. Butenandt, R. Beckman, D. Stamm, E. Hecker*, Z. Naturforsch. *B 14*, 283 (1959).
[2] Cf. also *F. Anders, E. Bayer*, Biol. Zentralbl. *78*, 584 (1959).
[3] *R. A. Steinbrecht*, Z. Zellforsch. *139*, 533 (1973).
[4] *K. E. Kaissling, H. J. Bestmann, G. Kassang, O. Vostrowsky*, Nature, in press.
[5] *H. J. Bestmann, O. Vostrowsky, H. Paulus, W. Billmann, W. Stransky*, Tetrahedron Lett. *1977*, 121.
[6] Bombykal has also been found to be a possible intermediate in the enzymic inactivation of bombykol on the male antennae: *G. Kasang*, Int. Congr. Biochem., Hamburg, July 25—31, 1976.
[7] *G. Kasang, G. Göldner, N. Weiss*, J. Chromatogr. *59*, 393 (1971).
[8] For the electrophysiologically determined content of bombykol in the scent glands cf. *R. A. Steinbrecht*, Vergl. Physiol. *48*, 341 (1964).
[9] Due to losses during extraction and purification, which amounted to about 50% in the case of bombykal, we can not rule out the presence of very small amounts of other stereoisomers of the aldehyde in the scent glands.
[10] Finnigan 3200E Quadrupole Mass Spectrometer with Finnigan 6000 Data System.
[11] *D. Schneider*, J. Insect Physiol. *8*, 15 (1962).
[12] *M. Silverstein* in *M. Beroza:* Pest Management with Insect Sex Attractants, ACS Symp. Ser. No. 23. American Chemical Society, Washington 1970.
[13] *H. J. Bestmann*, Conference of the Dtsch. Ges. Fettwissenschaft, Würzburg, September 20—23, 1977.—Cf. also the results of field experiments with mixtures of (*Z*)- and (*E*)-alkenol acetates and with alkenols and alkenals: *J. A. Klun, O. L. Chapman, K. C. Mattes, P. W. Wojtkowski, M. Beroza, P. E. Sonnet*, Science *181*, 661 (1973); *A. K. Minks, S. Voerman*, Entomol. Exp. Appl. *16*, 541 (1973); *C. R. Gentry, M. Beroza, J. L. Blythe, B. A. Bierl*, J. Econ. Entomol. *67*, 607 (1974); *C. J. Sanders*, Environ. Entomol. *5*, 868 (1976).

Triptycenophanes—Synthesis *via* "Double Nonbenzylic Sulfone Pyrolysis"[1]

By *Fritz Vögtle* and *Philippe Koo Tze Mew*[*]

The tricyclic molecular skeleton *(1)*, called "paddlane"[2], has been the object of numerous synthetic studies which have been partly successful in only isolated cases *(2)*, *(3)*, *(4)*[2a–c].

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(1) (2) (3) (4)

We now describe novel synthetic pathways leading to previously unknown triptycene hydrocarbons *(9)* bearing a 9,10 alkano bridge, related Diels-Alder adducts *(10)*, and their stereochemistry.

Syntheses:

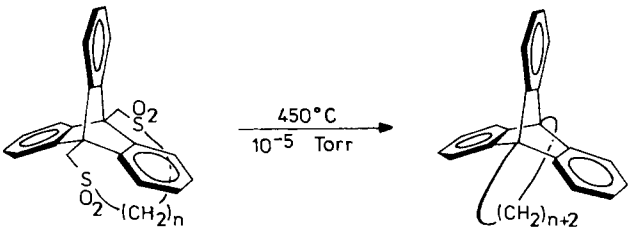
Starting from dithia(9,10)anthracenophanes *(5)* obtainable by methods utilizing the dilution principle, and the bissulfones *(6)* prepared therefrom by oxidation with *m*-chloroperbenzoic acid, Diels-Alder addition with benzyne leads to the triptycenophane derivatives *(8)* in 5% yield (cf. Table 1).



(5), X = S *(a)*: n = 8 *(7)*

(6), X = SO_2 *(b)*: n = 12

Surprisingly, "double nonbenzylic sulfone pyrolysis"[3] proceeds *via* recombination of the aliphatic bridge with the methylene groups located at the bridgehead to give the hydrocarbon *(9b)* of [(*n*+2).2.2]paddlane type, albeit in only low yield[4] (cf. Table 1).



(8) *(a)*: n = 8 *(9)*

(b): n = 12

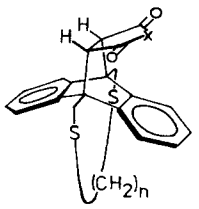
The alternative approach—synthesis of [*n*+2](9,10)triptycenophane *(9)* *via* pyrolysis of the bissulfone *(6)*—proceeded only as far as *(7)* whose reaction with benzyne failed to give *(9)*, probably owing to excessively high ring strain.

Attempted cycloaddition of benzyne to the bissulfides *(5)* was also unsuccessful since the C—S bond was broken. In contrast, the analogous Diels-Alder addition of dienophiles such as maleic anhydride or *N*-phenylmaleimide to the anthracenophanes *(5)* to *(10)* proved possible.

Table 1. Melting points and ^{1}H-NMR data of the compounds synthesized.

	M.p. [°C]	Yield [%]	^{1}H-NMR (90 MHz, δ values in $CDCl_3$/TMS int.) CH (Phenylene)	CH_2 (Bridgehead)
(5a) [b]	158—160	29	8.50, 7.62 [c]	4.85 (s) [d]
(5b) [b]	108—109	24	8.47, 7.57 [c]	4.82 (s) [d]
(6a) [b]	320—322	70—90	8.54, 7.81 [c]	5.58 (s) [d]
(6b) [b]	227—229	61—80	8.48, 7.75 [c]	5.50 (s) [d]
(7a)	171—172	52	8.35, 7.46 [c]	3.78 (t) [d]
(7b)	188—200 [e]	10	8.23, 7.33 [c]	3.62 (t) [d]
(8a)	>350 [f]	4	8.14, 7.39 (AA'BB', 8H) 6.98 (s, 4H)	5.02 (s) [d]
(8b)	368—370	5	8.08, 7.33 (AA'BB', 8H) 7.02 (AA'BB', 4H)	5.04 (s) [d]
(9b)	190—195	3	7.59 (m, 4H), 7.07 (m, 6H), 6.77 (m, 2H)	3.00 (t) [d]
(10a) *n*=8	198—200 [f]	2	8.14, 7.47 (m, 8H)	4.51, 3.83 (q) [g]
(10a) *n*=12	202—204 [f]	53	7.89, 7.40 (m, 8H)	4.29, 3.76 (q) [g]
(10b) *n*=8	188—190 [f]	4	8.15, 7.46 (m, 11H) 6.50 (m, 2H)	4.67, 3.91 (q) [g]
(10b) *n*=12	199 [f]	35	7.90, 7.39 (m, 11H) 6.50 (m, 2H)	4.46, 3.86 (q) [g]
(11) [b]	273—274	81	7.35 (m, 11H), 6.51 (m, 2H)	—
(12) [b]	290—295	2	7.84, 7.06 (m, 12H)	4.09 (s) [d]
(13a)	258—260 [f]	60	7.90, 7.34 (m, 8H)	4.10, 3.84 (q) [g]
(13b)	236—238 [f]	40	7.30 (m, 18H)	4.21, 4.09 (q) [g]

[a] The structures of all the compounds given were confirmed by elemental analysis and/or high resolution mass spectra and ^{1}H-NMR spectra.
[b] ^{1}H-NMR spectrum recorded at 60 MHz.
[c] AA'BB' system (8H).
[d] 4H.
[e] Owing to the small quantities obtained this compound was used without complete purification; no contamination can be detected in the ^{1}H-NMR spectrum.
[f] Decomposition.
[g] $J_{AB} \approx 13$—14 Hz (4H).



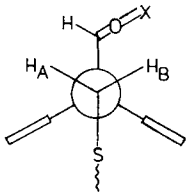
(10a), X = O

(10b), X = NC_6H_5

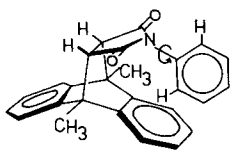
n = 8, 12

Stereochemistry and steric interactions: In the triptycenophanes *(8a)* and *(8b)* the triptycene system cannot rotate under the $(CH_2)_8$ or $(CH_2)_{12}$ bridge. This follows both from the ^{1}H-NMR spectrum, which exhibits two groups of signals in the intensity ratio 2:1 for the aromatic protons, and from consideration of space-filling models which show the bridge to be clamped between two of the three benzene rings[5]. The same applies to the hydrocarbon *(9b)*, whose UV absorption (λ_{max} = 280, 274, and 265 nm) shows a bathochromic shift relative to that of 9,10-dimethyltriptycene (276, 267, 258 nm; in isooctane); furthermore the longest wavelength maximum shows a significantly lower extinction.

As in *(8)* and *(9)*, the chain is fixed in the Diels-Alder adduct *(10)*, on the side opposite the former dienophile. This backside attack in Diels-Alder cycloaddition seems reasonable on steric grounds. The bridge CH_2 protons are diastereotopic and appear as an AB system, as is clear from the Newman projection *A* of *(10)*:



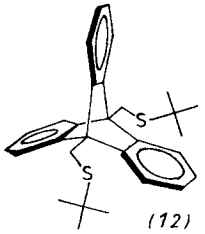
(10A)



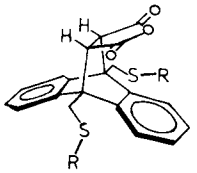
(11)

Once again the triptycene-type structural unit of *(10)* is unable to pass under the—too short—bridge, not even on warming to 120 °C (slow decomposition starts at higher temperature). The upfield shift of the phenyl protons *ortho* to nitrogen in the *N*-phenylmaleimide adduct *(10b)* is remarkable. Space-filling models show that these protons should come into the region of the shielding anisotropic effect of the benzene ring lying below them by rotation of the phenyl group about the C—N bond. A similar situation is expectedly observed in the open-chain compound *(11)* obtainable analogously by Diels-Alder reaction of 9,10-dimethylanthracene with *N*-phenylmaleimide.

A further insight into the stereochemistry of the bridged triptycene system is provided by comparisons with the open-chain analogs *(12)* and *(13)*.



(12)



(13a), R = $C(CH_3)_3$

(13b), R = $CH_2C_6H_5$

In the *tert*-butyl compound *(12)* rotation about the triptycenyl—CH_2S bond is sterically hindered: the resonance signals of the H_α,H_β protons of the aromatic rings show broadening, the effect being more pronounced for the α part than for the β part. On cooling, the α part is observed to split into two signals in the intensity ratio 2:1 since rotation of the CH_2StBu group is frozen in [rotational barrier $\Delta G_{Tr}^{\neq} \approx 15.7$ kcal/mol (65.7 kJ/mol)]. These results are in accord with those obtained for 9,10-bis(chloromethyl)triptycene[6]. The corresponding rotation is less hindered in the benzyl compound *(13b)* [$\Delta G_c^{\neq} < 10$ kcal/mol (42 kJ/mol)]. The NMR signals of the aromatic protons are not broadened; the diastereotopic bridgehead CH_2 protons absorb as an AB system.

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CAS Registry numbers:
(5a), 65121-51-9; *(5b)*, 65121-52-0; *(6a)*, 65121-53-1; *(6b)*, 65121-54-2; *(7a)*, 65121-55-3; *(7b)*, 65121-56-4; *(8a)*, 65121-57-5; *(8b)*, 65121-58-6; *(9b)*, 65121-59-7; *(10a)* (n=8), 65121-60-0; *(10a)* (n=12), 65121-61-1; *(10b)* (n=8), 65121-62-2; *(10b)* (n=12), 65121-63-3; *(11)*, 65121-64-4; *(12)*, 65121-65-5; *(13a)*, 65121-66-6; *(13b)*, 65121-67-7

[1] C—C Bond Formation by Sulfone Pyrolysis, Part 13. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We are grateful to Dr. *G. Hohner* for valuable discussions.—Part 12: *L. Rossa, F. Vögtle*, J. Chem. Res. (S) *1977*, 264.

[2] a) *R. Helder, H. Wynberg*, Tetrahedron Lett. *1973*, 4321; b) *E. H. Hahn, H. Bohm, D. Ginsburg, ibid. 1973*, 507; c) *T. Mori, K. Kimoto, M. Kawanisi, H. Nozaki, ibid. 1969*, 3653; d) review: *J. F. Liebman, A. Greenberg*, Chem. Rev. *76*, 349 (1976).

[3] Concerning "double nonbenzylic sulfone pyrolysis" in the more favorable *o*-terphenyl system, cf. *F. Vögtle, L. Rossa*, Tetrahedron Lett. *1977*, 3577.

[4] Formation of *(9a)* is certain, but purification runs into difficulties. In contrast to *(9b)*, the shorter bridge in *(9a)* cannot be constructed with space-filling models.

[5] In the ^{1}H-NMR spectrum, *(7a)* shows a very strong upfield shift of the four central CH_2 bridge protons: δ = 0.0. In the correspondingly bridged parabenzenophane these protons absorb at lower field: δ = 0.7.

[6] Review: *M. Oki*, Angew. Chem. *88*, 67 (1976); Angew. Chem. Int. Ed. Engl. *15*, 87 (1976).

Quaternary Ammonium Salts as Catalysts of Nucleophilic Substitution Reactions in a Solid-Liquid Two-Phase System

By *Andrzej Jończyk, Maria Ludwikow*, and *Mieczyslaw Mąkosza*[*]

Macrocyclic polyethers (crown ethers) form stable complexes with alkali metal cations, and are able to solubilize many inorganic salts in moderately polar solvents[1,2]. The anions of such solubilized salts are poorly solvated and exhibit high activity, hence the name "naked anions"[3]. For practical purposes the use of 5—10 mol-% of crown ethers suffices for complete conversion of substrates[1-3]. Thus, crown ethers evidently effect continuous transfer of the anions from the solid phase into solution. This process is similar to a "phase-transfer" catalyzed[4] liquid-liquid reaction, and it might therefore be expected that in the liquid-solid system the reactions should also be catalyzed by the much less expensive tetraalkylammonium (TAA) salts.

In contrast to previous studies[2,4b] we have now found that lipophilic TAA salts do indeed catalyze the reactions of inorganic salts in a solid-liquid system[5]:

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$$R{-}X_{liquid} + MY_{solid} \xrightarrow[CH_3CN \text{ or } CH_2Cl_2]{\text{Aliquat 336}} R{-}Y_{liquid} + MX_{solid}$$

RX	MY	Solvent	t [a] [h]	Conversion [%] [b]
$C_6H_5CH_2Cl$	NaOAc	CH_3CN	4.5 [c]	100 [d]
$C_4H_9OSO_2CH_3$	NaOAc	CH_3CN	5.0	61
$C_6H_5CH_2Cl$	KSCN	CH_3CN	1.5	100 [e]
C_4H_9Br	KSCN	CH_3CN	2.0	98 [e]
$C_6H_5CH_2Cl$	KF	CH_3CN	25.0	30
$C_6H_5CH_2Cl$	KBr	CH_3CN	5.0	39
$C_4H_9OSO_2CH_3$	KNO_2	CH_2Cl_2	30.0	32
$C_6H_5CH_2Cl$	NaCN	CH_3CN	10.0	88

[a] We have not optimized the reaction time. [b] Determined by GLC. [c] After 1 h, conversion 81 %. [d] Without catalyst, conversion ≈10 %. [e] The same results with and without catalyst.

If a solution of alkyl halide or methanesulfonate in acetonitrile or dichloromethane with an excess of a dried and ground sodium or potassium salt (Table) and 1—3 % of Aliquat 336 (trade name for technical grade methyltrioctylammonium chloride) then a nucleophilic substitution takes place. The tabulated data evidence a strong catalytic effect of the quaternary ammonium compounds. The fact that they are somewhat less effective catalysts than crown ethers is, in our opinion, due to different structures of solubilized ion pairs (cation-anion interactions).

In the case of specific examples suitable choice of catalyst and optimization of the reaction conditions may greatly improve the yields.

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CAS Registry numbers:
$C_6H_5CH_2Cl$, 25168-05-2; $C_4H_9OSO_2CH_3$, 1912-32-9; C_4H_9Br, 109-65-9; NaOAc, 127-09-3; KSCN, 333-20-0; KF, 7789-23-3; KBr, 7758-02-3; KNO_2, 7758-09-0; NaCN, 143-33-9; methyltrioctylammonium chloride, 5137-55-3

[1] *C. J. Pedersen, H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. Int. Ed. Engl. *11*, 16 (1972).
[2] *G. W. Gokel, H. D. Durst*, Synthesis *1976*, 168.
[3] *C. L. Liotta, H. P. Harris*, J. Am. Chem. Soc. *96*, 2250 (1974).
[4] a) *C. M. Starks*, J. Am. Chem. Soc. *93*, 195 (1971); b) *C. M. Starks, R. M. Owens, ibid. 95*, 3613 (1973); c) cf. also *E. V. Dehmlow*, Angew. Chem. *89*, 521 (1977); Angew. Chem. Int. Ed. Engl. *16*, 493 (1977).
[5] Some patents claim synthesis of isocyanates from alkyl halides in a solid-liquid system catalyzed by TAA chlorides, *e.g. Y. Nadachi, M. Kogura*, Jpn. Pat. 7595289 (1975); Chem. Abstr. *84*, 164852 (1976).

Reactive Derivatives of Aliphatic *N*-Sulfinylamines—Alkylation of *N*-Sulfinylalkylamines and Bis(*tert*-butyl)-sulfur Diimide

By *Günter Kresze* and *Michael Rössert*[*]

N-Sulfinyldimethylimmonium hexachloroantimonate is a known compound[1]. We have now found that compounds of this type are readily accessible by alkylation of aliphatic *N*-sulfinylamines *(1)* with trialkyloxonium tetrafluoroborates *(2)*:

$$R^1NSO + R^2_3O^{\oplus}BF_4^{\ominus} \longrightarrow \begin{matrix} & & R^1 \\ & & \diagdown \\ & & N^{\oplus}{=}SO \\ & & \diagup \\ & & R^2 \end{matrix} BF_4^{\ominus} + R^2_2O$$

(1) *(2)*

(3a), $R^1 = R^2 = CH_3$
(3b), $R^1 = C_2H_5$, $R^2 = CH_3$

Thus the immonium salt *(3a)* is obtained in 97 % yield by direct reaction of the amine without solvent at 15 °C [m.p. 72—75 °C; ^{1}H-NMR (in CD_3NO_2): $\delta = 4.02$ (6H) s]. The ethyl derivative can be prepared analogously [oil; ^{1}H-NMR (in CD_3CN): $\delta = 1.52$ (3H) t, 3.82 (3H) s, 4.35 (2H) q, $J = 7$ Hz].

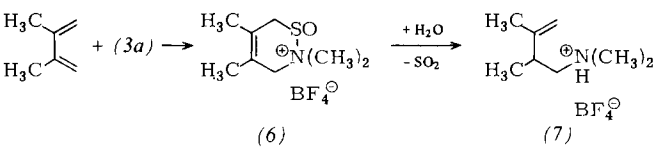
N,N'-Bis(*tert*-butyl)sulfur diimide *(4)* can also be monoalkylated by the same procedure:

$$t\text{BuN=S=N}t\text{Bu} \xrightarrow{[R_3O]BF_4} t\text{BuN}^{\oplus}{=}\text{S=N}t\text{Bu}\ BF_4^{\ominus}$$
$$\quad\quad R$$

(4) *(5a)*, R = CH_3
(5b), R = C_2H_5

The salts *(5a)* [m.p. 124 °C (dec.); ^{1}H-NMR (in CD_3NO_2): $\delta = 1.64$ (9H) s, 1.73 (9H) s, 3.71 (3H) s] and *(5b)* [m.p. 108 °C (dec.); ^{1}H-NMR (in CD_3NO_2): $\delta = 1.37$ (3H) t, 1.66 (9H) s, 1.73 (9H) s, 4.35 (2H) q, $J = 7$ Hz] were synthesized in 91 and 92 % yield, respectively.

As electron-deficient *N*-sulfinyl compounds[2], the immonium tetrafluoroborates *(3)* are very suitable for cycloaddition reactions. For example, *(3a)* reacts cleanly with 2,3-dimethylbutadiene in acetonitrile to form the adduct *(6)* [m.p. 86—88 °C; ^{1}H-NMR (in CD_3NO_2): $\delta = 1.83$ (6H) s (br) ($CH_3C{=}$), 3.16 and 3.27 (6H) s (CH_3N), 3.60—4.60 (4H) m (CH_2S and CH_2N)].



(6) *(7)*

Hydrolysis of *(6)* leads to the (1-buten-4-yl)ammonium salt *(7)*, m.p. 90—92 °C.

General procedure

N-Sulfinylalkylamine (13 mmol) is added to trialkyloxonium tetrafluoroborate (10 mmol) at 15 °C and the mixture is allowed to react at this temperature for 10 h. The crude product is washed [*(3a)*] or extracted [*(3b)*] with a large amount of dichloromethane and dried *in vacuo*.

The preparation of *(5a)* and *(5b)* can be performed in analogous manner except that dichloromethane is used as solvent. The crude product can be recrystallized from dichloromethane/ether.

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CAS Registry numbers:
(1), 4291-05-8; *(2a)*, 420-37-1; *(2b)*, 368-39-8; *(3a)*, 65149-75-9; *(3b)*, 65149-77-1; *(4)*, 2056-74-8; *(5a)*, 65185-55-9; *(5b)*, 65149-79-3; *(6)*, 65167-93-3; *(7)*, 65149-81-7; 2,3 dimethylbutadiene, 513-81-5

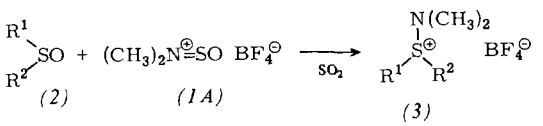
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Organisch-chemisches Institut der Technischen Universität München
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[1] *W. Warthmann, A. Schmidt*, Z. Anorg. Allg. Chem. *418*, 61 (1975).
[2] Review: *G. Kresze, W. Wucherpfennig*, Angew. Chem. *79*, 109 (1967); Angew. Chem. Int. Ed. Engl. *6*, 149 (1967).

A New Synthetic Entry to Mono-, Bis-, and Tris-(amino)sulfonium Salts

By *Günter Kresze* and *Michael Rössert*[*]

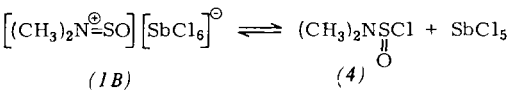
Reactive *N*-sulfinylamine derivatives are transformed into sulfimides on reaction with sulfoxides. *N*-Sulfinyldimethylimmonium tetrafluoroborate *(1A)* synthesized by us on a previous occasion[1] gives monoaminosulfonium tetrafluoroborates such as *(3a)*; it can react analogously with *N,N*-dimethylmethanesulfinamide *(2b)* to give the bis(amino)sulfonium salt *(3b)* or with *N,N'*-sulfinylbis(dimethylamine) to form the tris(amino)sulfonium salt *(3c)*.



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

(a): $R^1 = R^2 = CH_3$
(b): $R^1 = CH_3$, $R^2 = N(CH_3)_2$
(c): $R^1 = R^2 = N(CH_3)_2$

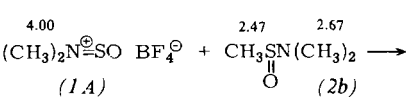
The hexachloroantimonate *(3d)* corresponding to *(3c)* can be prepared analogously; however, in the case of the $SbCl_6$ salt *(1B)* corresponding to *(1A)* it would appear that retrocleavage can have an interfering effect. Whereas *(1A)* fails to react with diphenyl sulfoxide, fast reaction to form dimethylaminosulfinyl chloride *(4)* and an addition compound of diphenyl sulfoxide and antimony pentachloride is observed with *(1B)*.



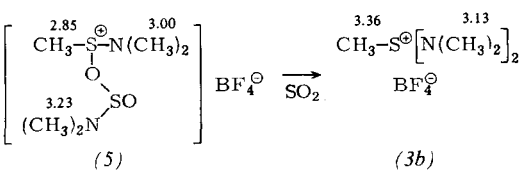
(1B) *(4)*

The adduct assumed to occur as intermediate in the reactions of *(1A)*, for instance *(5)*, appears to be relatively stable: the ^{1}H-NMR spectra of a solution of *(1A)* and *(2b)* in CD_3NO_2 show a distinct shift of the signals of the reactants immediately upon mixing, while the signals of the product *(3b)* appear only slowly (cf. δ values in reaction scheme).

Reaction to form *(3b)* is complete within 1 h at room temperature.



(1A) *(2b)*



(5) *(3b)*

The hexachloroantimonates corresponding to tetrafluoroborates *(3)* have already been prepared by another method[2]. The alternative method which we now propose provides a facile entry to the aminosulfonium salts which are resistant to ethanol [*(3a)*, *(3b)*] and to water [*(3b)*].

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Procedure

An equivalent amount of the sulfinyl compound *(2)* is added to a 2 M solution of *(1A)* or *(1B)* in acetonitrile at −25 °C; the mixture is allowed to warm over a period of 1 h and then stirred for 2 h at room temperature. The solvent is drawn off in a water-pump vacuum and the residue dissolved in CH_2Cl_2. Insoluble material is filtered off and product *(3)* precipitated with ether.

In the case of *(3a)* the precipitate is washed with warm ethanol, yield 46 %, m.p. 150—155 °C; ^{1}H-NMR (in CD_3NO_2): $\delta = 2.98$ (6H) s, 3.08 (6H) s.—*(3b)* is recrystallized from ethanol, yield 67 %, dec. 185—190 °C after yellow coloration above 160 °C; ^{1}H-NMR (in CD_3NO_2); $\delta = 3.13$ (12H) s, 3.36 (3H) s.—*(3d)* is recrystallized from acetonitrile/ether, yield 20 %, dec. 160 °C after yellow coloration above 120 °C; ^{1}H-NMR (in CD_3CN): $\delta = 2.89$ (18H) s.

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CAS Registry numbers:
(1A), 65149-75-9; *(1B)*, 65185-69-5; *(2a)*, 67-68-5; *(2b)*, 920-56-9; *(2c)*, 3768-60-3; *(3a)*, 65168-00-5; *(3b)*, 65149-89-5; *(3c)*, 65149-90-8; *(3d)*, 57810-59-0; *(4)*, 26555-92-0; *(5)*, 65149-92-0

[1] *G. Kresze, M. Rössert*, Angew. Chem. *90*, 61 (1978); Angew. Chem. Int. Ed. Engl. *17*, 63 (1978).
[2] *W. Warthmann, A. Schmidt*, Z. Anorg. Allg. Chem. *418*, 57 (1975).

New Compounds from 1,4-Diaza-1,3-dienes and Iron Carbonyls: Hexacarbonyl(1,4-diazadiene)diiron and Substituted 2(3*H*)-Imidazolones[**]

By *Hans-Werner Frühauf, Armin Landers, Richard Goddard,* and *Carl Krüger*[*]

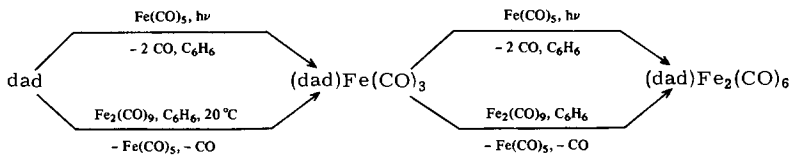
In the presence of 1,4-diaza-1,3-dienes *(1)*, "dad", the tricarbonyliron complexes *(2)*, (dad)$Fe(CO)_3$, are formed photochemically from $Fe(CO)_5$ and thermally from $Fe_2(CO)_9$[1, 2]. Adopting this approach, we attempted to prepare a series of partly known complexes *(2)* in order to obtain the corresponding (dad)(diene)Fe(CO) complexes[3] by photochemical reaction with dienes[4]. In most cases, however, we did not only isolate *(2)* but in addition the novel dinuclear complexes *(3)*, (dad)$Fe_2(CO)_6$, formed in a secondary reaction.

For instance, photolysis of $Fe(CO)_5$ with *(1b)* (molar ratio 2:1) in *n*-hexane gives the diiron complex *(3b)* in over 90 % yield after a single recrystallization from *n*-hexane.

As a result of unsymmetrical coordination to the $Fe_2(CO)_6$ unit, the signals of the symmetrical dad ligands appear double in the ^{1}H-NMR spectra of complexes *(3)*: *e.g. (3a)* in C_6D_6: 1 H (d) at $\delta = 6.87$ and 2.87 with $J = 1.9$ Hz and 9 H (s) at

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[++] X-Ray structure analysis.

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



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

$\delta = 1.25$ and 0.82. The IR spectra show five or six CO stretching bands between *ca.* 2060 and 1940 cm^{-1} (Table 1) with an intensity distribution resembling that for other unsymmetrical $Fe_2(CO)_6$ complexes[5].

Table 1. IR data of some compounds *(3)* and *(4)*, ν_{CO} [cm^{-1}].

dad *(1)*		R^1/R^2	*(3)* [a]	*(4)* [b]
	*(a)*	H /*t*-C_4H_9	2057, 2007, 1984, 1970, 1946	1664
	(b)	H /C_6H_{11}	2059, 2007, 1987, 1973, 1948 (sh), 1945	—
	(c)	CH_3/C_6H_4-*p*-OCH_3	2062, 2007, 1195, 1979, 1945, 1941	1675, 1640

[a] In *n*-hexane. [b] ν_{CO} and $\nu_{C=C}$ in KBr; *(4a)* in *n*-hexane: 1689, 1687 (sh) cm^{-1}.

The structure of *(3b)* could be elucidated by X-ray structure analysis [cell data: $a = 14.724(3)$, $b = 10.576(2)$, $c = 15.686(5)$ Å, $\beta = 112.63(2)°$, space group $P2_1/c$, $Z = 4$; 4874 reflections of which 1913 were considered unobserved (2σ); $R = 0.036$ ($R_w = 0.040$)]. While nitrogen atom N1 of the dad ligand occupies an axial position at Fe1 by means of its lone pair and is doubly bonded to C1 with a remarkably short bond length, N2 forms an unsymmetrical bridge between the Fe—Fe system displaying a characteristic metal-metal internuclear distance (Fig. 1). The N2C2 group is therefore to be regarded as a three-electron donor to Fe2 and a one-electron donor to Fe1. This situation is not reflected in different N—C bond lengths to the cyclohexyl groups (1.492(4) and 1.488(4) Å). The coplanarity of the conjugated system N1—C1—C2—N2 (±0.05 Å) is only negligibly perturbed by the unsymmetrical complexation (dihedral angle N1—C1—C2—N2 = 12.2°).

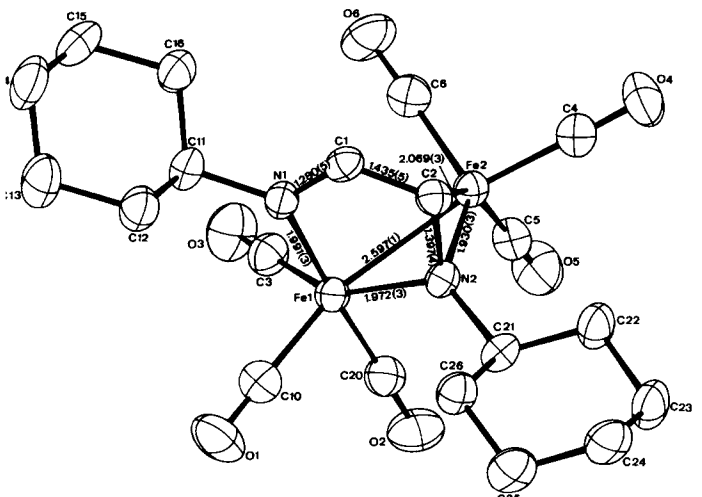
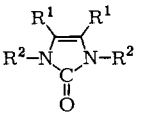


Fig. 1. Molecular structure of hexacarbonyl(1,4-dicyclohexyl-1,4-diazabutadiene)diiron *(3b)* and numbering of the atoms.

The formation of *(2)* competes with transformation of some dad ligands of the open-chain 1,4-diazabutadiene type into *N,N'*-disubstituted 2(3*H*)-imidazolones *(4)* by CO insertion; compounds *(4)* can easily be separated from the mixture of *(2)* and *(3)* by chromatography. Imines of 2-acylpyridines do not undergo this competing reaction.



(4a), R^1 = H, R^2 = *t*-C_4H_9
(4c), R^1 = CH_3, R^2 = C_6H_4-*p*-OCH_3

Compound *(4a)* is formed particularly readily during the preparation of *(2a)*, and like the latter it sublimes well *in vacuo*. In *n*-hexane its CO stretching vibration appears at 1689 cm^{-1}. In the case of *(2a)*, we were unable to observe this IR band [2] or signal doubling in the ^{1}H-NMR spectrum of the coordinated ligand, from which an unsymmetrical n,π coordination was previously inferred.

Procedure

(1c) (1.0 g, 3.37 mmol) and $Fe(CO)_5$ (0.91 ml, 1.33 g, 6.76 mmol) in degassed benzene (100 ml) are irradiated under argon in an immersion well apparatus (glass or quartz) with a Hg high-pressure lamp for 30 h. Alternatively, *(1c)* (1.0 g) and $Fe_2(CO)_9$ (2.44 g, 6.7 mmol) in benzene (100 ml) can be stirred at room temperature for 48 h. The filtered reaction solution is evaporated down (about 1.6 g of residue) and chromatographed under argon on de-aerated silica gel. A mixture of *(2c)* and *(3c)* is eluted with benzene, and then *ca.* 450 mg of *(4c)* (m.p. from ethyl acetate 168—169 °C) with ethyl acetate. The fraction containing *(2c)* and *(3c)* can either be transformed into pure *(2c)* in an autoclave at 50 °C under 50 bar of CO (700—750 mg from *n*-hexane) or evaporated down in order to wash out the *(2c)*, which is highly soluble in *n*-hexane. Yield of *(3c)* *ca.* 600 mg.

In the corresponding reaction of *(1a)* the mixture of *(2a)* and *(3a)* obtained by chromatography can be separated by sublimation of *(2a)*. *(4a)* is recrystallized from *n*-hexane, m.p. 113 °C (in sealed tube)[6].

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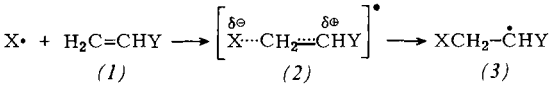
CAS Registry numbers:
(1a), 30834-74-3; *(1b)*, 3673-06-1; *(1c)*, 19215-52-2; *(2a)*, 65036-35-3; *(2b)*, 54446-63-8; *(2c)*, 65016-01-5; *(3a)*, 65045-67-2; *(3b)*, 65059-34-9; *(3c)*, 65036-39-7; *(4a)*, 65015-69-2; *(4c)*, 65015-68-1; $Fe(CO)_5$, 13463-40-6; $Fe_2(CO)_9$, 15321-51-4

[1] *S. Otsuka, T. Yoshida, A. Nakamura*, Inorg. Chem. 6, 20 (1967).
[2] *H. tom Dieck, A. Orlopp*, Angew. Chem. *87*, 246 (1975); Angew. Chem. Int. Ed. Engl. *14*, 251 (1975).
[3] Cf. *M. A. DePaoli, H.-W. Frühauf, F.-W. Grevels, E. Koerner von Gustorf, W. Riemer, C. Krüger*, J. Organomet. Chem. *136*, 219 (1977).
[4] *H.-W. Frühauf, F.-W. Grevels, A. Landers*, unpublished.
[5] *F.-W. Grevels, E. Koerner von Gustorf*, Justus Liebigs Ann. Chem. *1975*, 547.
[6] All compounds *(2)*, *(3)*, and *(4)* mentioned gave correct elemental analyses.

Reactivity of Alkenes in Free-Radical Additions[**]

By *Bernd Giese* and *Wolfgang Zwick*[*]

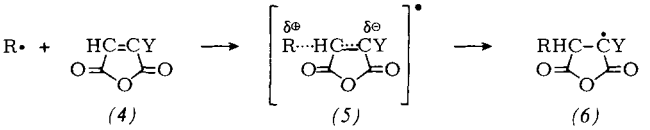
The preferred attack of radicals at the lower alkylated carbon atoms of alkenes is usually explained in terms of a stabilizing influence of alkyl groups on radicals[1]. If the stability of the radicals increases with increasing degree of alkylation on the radical carbon atom and this effect becomes significant in the transition state, then the reactivity of the alkene in radical additions ought to increase with its degree of alkylation. Indeed, propene is more rapidly attacked than ethylene by electron deficient radicals such as $Cl^{\bullet}$[2a], $Br^{\bullet}$[2b], $HO^{\bullet}$[2c], $F_2N^{\bullet}$[2d] or $(CF_3)_2FC^{\bullet}$[2e]. The gradation of reactivity of the olefins *(1)*, however, is no unequivocal proof of the greater stability of the secondary radical *(3b)* compared to the primary radical *(3a)*, because the difference in rate of addition of electron deficient, electrophilic radicals X• can also be due to the polar effect[1,4] of the methyl substituents (Y = CH_3) in the transition state *(2)*.



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

(a): Y = H
(b): Y = CH_3

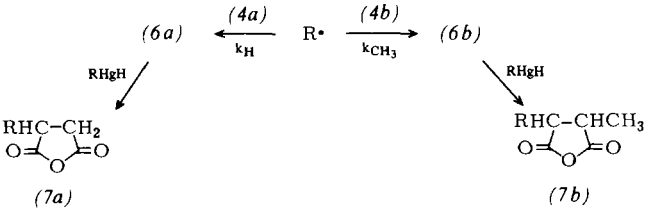
In order to differentiate between the polar effect and radical stabilization, the relative reactivities of maleic anhydride *(4a)* and methylmaleic anhydride *(4b)* towards electron rich, nucleophilic[5] alkyl radicals R• was determined. In these additions the electron-donating methyl group (Y = CH_3) exerts a counteracting influence on the polar effect in the transition state *(5)* on the one hand, and on the stability of the adduct radical *(6)* on the other.



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

(a): Y = H
(b): Y = CH_3

For measurement of the relative reactivities the organomercury salts RHgX were allowed to react with $NaBH_4$ in chloroform in the presence of at least a 20-fold excess of the olefin mixture *(4a)*/*(4b)*. Under these conditions alkyl radicals are formed which add in high yields to the olefins *(4a)* and *(4b)*[6]. The H-capturing products *(7a)* and *(7b)* are formed quantitatively from the adduct radicals *(6a)* and *(6b)*[6],



(7a) *(7b)*

$$\frac{k_H}{k_{CH_3}} = \frac{[(7a)]\,[(4b)]}{[(7b)]\,[(4a)]} \qquad (I)$$

so that the ratio of the rate constants k_H/k_{CH_3} for the individual radicals can be determined according to Eq. (I)[5].

The difference in the activation parameters for the reactions with olefins *(4a)* and *(4b)* were determined from measurements carried out between 246 and 298 K. These data, together with the competition constants k_H/k_{CH_3} at 263 K, are listed in Table 1.

Table 1. Competition constants at 263 K (mean error ±10%), differences in activation enthalpies [kJ mol^{-1}] (mean error ±2 kJ mol^{-1}) and differences in activation entropies [JK^{-1} mol^{-1}] (mean error ±6 JK^{-1} mol^{-1}) for the competing addition of alkyl radicals R• to maleic anhydride *(4a)* and methylmaleic anhydride *(4b)* in $CHCl_3$.

Radical R•	k_H/k_{CH_3}	$\Delta H^{\ddagger}_{CH_3} - \Delta H^{\ddagger}_{H}$	$\Delta S^{\ddagger}_{CH_3} - \Delta S^{\ddagger}_{H}$
$(CH_3)_3C^{\bullet}$	13.6	0.0	−21
$c\text{-}C_6H_{11}^{\bullet}$	9.8	1.2	−15
$n\text{-}C_5H_{11}CH_2^{\bullet}$	6.5 [a]		

[a] The mean error here is ±20%. Because of this large error and simultaneously small competition constants, determination of the activation parameters was dispensed with.

The competition constants k_H/k_{CH_3} (Table 1) show that maleic anhydride reacts distinctly more rapidly with alkyl radicals than the higher alkylated methylmaleic anhydride[7]. Formation of the secondary radical *(6a)* is thus energetically more favorable than that of the tertiary radical *(6b)*. Hence, the radical stabilization effect of a methyl group on the rate of radical addition is so slight that the polar effects, and in the case of bulky groups also the steric effects, of the alkyl substituents predominate.

The gradation of reactivity in the case of electrophilic radicals[2] and the increase in selectivity on going from primary *n*-hexyl through the secondary cyclohexyl to the *tert*-butyl radical shows (Table 1) that the reactivity of differently alkylated alkenes largely depends upon the nucleophilicity of the radicals. Whereas electron deficient radicals react more rapidly with higher alkylated alkenes[2] electron rich alkyl radicals react more rapidly with lower alkylated alkenes (Table 1). It is therefore also understandable that the only slightly nucleophilic methyl radical adds to ethylene, propene and 2-methylpropene almost equally rapidly[8].

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CAS Registry numbers:
(1a), 74-85-1; *(1b)*, 115-07-1; *(3a)* (X = Cl), 16519-99-6; *(3a)* (X = Br), 16520-00-6; *(3a)* (X = OH), 4422-54-2; *(3a)* (X = F_2N), 65167-95-5; *(3a)* (X = $(CF_3)_2FC$), 65149-62-4; *(3b)* (X = Cl), 41895-36-7; *(3b)* (X = Br), 65149-63-5; *(3b)* (X = OH), 7055-10-9; *(3b)* (X = F_2N), 65149-64-6; *(3b)* (X = $(CF_3)_2FC$), 65149-65-7; *(4a)*, 108-31-6; *(4b)*, 616-02-4; *(6a)* (R = $(CH_3)_3C$), 65149-66-8; *(6a)* (R = $c\text{-}C_6H_{11}$), 65149-67-9; *(6a)* (R = $n\text{-}C_5H_{11}CH_2$), 65149-68-0; *(6b)* (R = $(CH_3)_3C$), 65149-69-1; *(6b)* (R = $c\text{-}C_6H_{11}$), 65149-70-4; *(6b)* (R = $n\text{-}C_5H_{11}CH_2$), 65167-97-7; *(7a)* (R = $(CH_3)_3C$), 52685-36-6; *(7a)* (R = $c\text{-}C_6H_{11}$), 5962-96-9; *(7a)* (R = $n\text{-}C_5H_{11}CH_2$), 46201-48-3; *(7b)* (R = $(CH_3)_3C$), 65149-71-5; *(7b)* (R = $c\text{-}C_6H_{11}$), 51953-01-6; *(7b)* (R = $n\text{-}C_5H_{11}CH_2$), 65149-72-6; $Cl^{\bullet}$, 22537-15-1; $Br^{\bullet}$, 10097-32-2; $HO^{\bullet}$, 3352-57-6; $F_2N^{\bullet}$, 3744-07-8; $(CF_3)_2FC^{\bullet}$, 3170-79-4; $(CH_3)_3C^{\bullet}$, 1605-73-8; $c\text{-}C_6H_{11}^{\bullet}$, 3170-58-9; $n\text{-}C_5H_{11}CH_2^{\bullet}$, 2679-29-0

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[2] a) *A. K. E. Hagopian, J. H. Knox, E. A. Thompson*, Bull. Soc. Chim. Belg. *71*, 764 (1962); b) *P. I. Abell*, Trans. Faraday Soc. *60*, 2214 (1964); c) *E. D. Norris, O. H. Stedman, H. Niki*, J. Am. Chem. Soc. *93*, 3570 (1971); d) *A. J. Dijkstra, J. A. Kerr, A. F. Trotman-Dickenson*, J. Chem. Soc. *A 1967*, 105; e) *L. L. T. Vertomen, J. M. Tedder, J. C. Walton*, J. Chem. Res. (S) *1977*, 18.
[3] *T. Mojelsky, Y. L. Chow*, J. Am. Chem. Soc. *96*, 4549 (1974).
[4] *C. Rüchardt*, Angew. Chem. *82*, 845 (1970); Angew. Chem. Int. Ed. Engl. *9*, 830 (1970).
[5] *B. Giese, J. Meister*, Angew. Chem. *89*, 178 (1977); Angew. Chem. Int. Ed. Engl. *16*, 178 (1977).

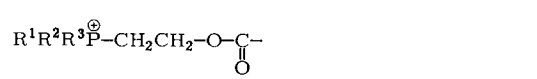
[6] a) *B. Giese, J. Meister*, Chem. Ber. *110*, 2588 (1977); b) *B. Giese, J. Meixner*, Tetrahedron Lett. *1977*, 2779.
[7] Since methylmaleic anhydride *(4b)* is attacked to at least 97% only at one olefinic carbon atom, then the competition constants k_H/k_{CH_3} must be halved and +5.8 [JK^{-1} mol^{-1}] added to the difference of the activation entropies, if the relative reactivities of the olefinic carbon atoms are to be compared instead of those of the alkenes.
[8] *R. J. Cvetanovic, R. S. Irwin*, J. Chem. Phys. *46*, 1694 (1967).

Syntheses with 2-Phosphonioethoxycarbonyl Protecting Groups: Peptide Synthesis in Water[**]

By *Horst Kunz*[*]

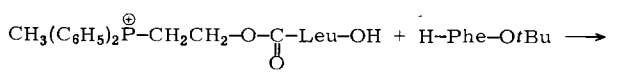
Peptide synthesis in aqueous solution has long been a principal aim of peptide chemistry[1]. Using water-soluble carbodiimides containing quaternary ammonium groups, *Sheehan et al.* succeeded in linking *N*-phthaloylglycine and glycine ethyl ester to form the dipeptide[2a] and in coupling a linear tripeptide to give the cyclohexapeptide[2b] in aqueous medium. Generalization of this synthetic pathway has hitherto been precluded by the insufficient solubility of the components undergoing coupling, especially the *N*-protected amino acids and peptides. Conventional protecting groups for the amino function, such as the Z and Boc groups, have hydrophobic character. *Pfaender et al.* recently reported the stepwise heterogeneous reaction of amino acid *N*-carboxylic anhydrides (NCA) with amino acids and peptides bound to polyethyleneimine in weakly alkaline aqueous phase[3]. This process, requiring no amino-protecting group, has no relevance to fragment condensation; moreover, the ready decomposition of NCAs in water would probably also interfere with reactions in homogeneous phase.

Peptide synthesis in homogeneous aqueous solution requires protecting groups which promote the water-solubility of the protected amino acids and peptides. 2-Phosphonioethoxycarbonyl (Peoc) groups[4] *(1)* have this property.

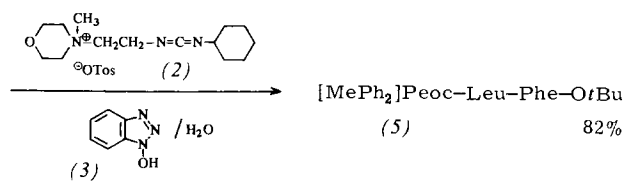


(1), R^1,R^2,R^3 = Alkyl, Aryl

The Peoc protecting groups can be removed from the protected amino functions under mildly basic conditions. This base lability is due to the CH acidity of the methylene group located in α-position to the phosphorus. Furthermore, in order to avoid even a weakly alkaline milieu for condensation, a modified Geiger-König technique[5] was employed in the experiments on peptide synthesis in aqueous solution: using the water soluble carbodiimide *(2)* in the presence of 1-hydroxybenzotriazole *(3)*, 2-(methyldiphenylphosphonio)ethoxycar-



(4) (= [$MePh_2$]Peoc-Leu-OH)

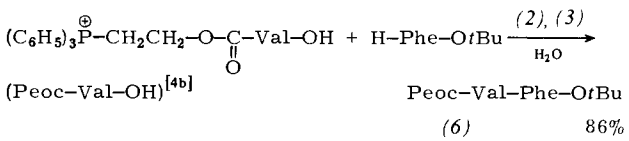


(2) *(3)*

[$MePh_2$]Peoc-Leu-Phe-O*t*Bu *(5)* 82%

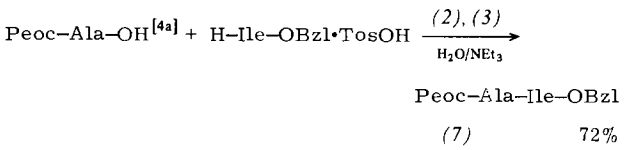
bonylleucine[4b] *(4)* can be linked with phenylalanine *tert*-butyl ester to give the Peoc-dipeptide ester *(5)* in good yield.

The low pH value of the reaction solution (*ca.* 4.5 initially and *ca.* 3.5 at conclusion of reaction) should also permit use of the more sensitive triphenylphosphonioethoxycarbonyl group. The synthesis of the two Peoc dipeptide esters *(6)* and *(7)* confirms this assumption.



(Peoc-Val-OH)[4b]

Peoc-Val-Phe-O*t*Bu *(6)* 86%



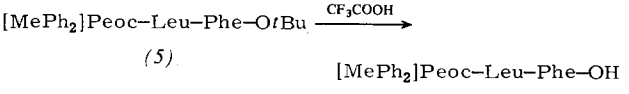
Peoc-Ala-Ile-OBzl *(7)* 72%

As demonstrated by compound *(7)*, the amino acid hydrosalts and triethylamine can be used instead of the free amino esters.

The Peoc-dipeptide esters *(5)*, *(6)*, and *(7)* precipitate as oils from the aqueous solutions. They were extracted with dichloromethane and transformed into the iodides by treatment with NaI in acetone prior to structural elucidation and calculation of yields because the Peoc-amino acids were used as bromides or chlorides and the carbodiimide *(2)* as *p*-toluenesulfonate.

In addition to the ester and urethane carbonyl bands (1715—1730 cm^{-1}) the IR spectra also contain the amide I band of the newly formed peptide bond at 1650—1670 cm^{-1}; the amide II band is observed at 1500—1550 cm^{-1} and a sharp band characteristic for phosphonium salts with aromatic ligands attached to phosphorus at 1435 cm^{-1}. In the ^{1}H-NMR spectra (in $CDCl_3$ rel. to TMS) the phenyl protons of the Peoc protecting group absorb at $\delta = 7.8$, and thus at significantly lower field than the aromatic protons of the phenylalanine in *(5)* and *(6)* ($\delta = 7.2$) and the benzyl ester in *(7)* ($\delta = 7.3$). Furthermore, the IR and ^{1}H-NMR spectra of *(5)* are identical in all essential details with those of the compound already prepared in dichloromethane[4b].

After transformation into its iodide, [$MePh_2$]Peoc-Leu-Phe-O*t*Bu prepared in CH_2Cl_2 by the Wünsch-Weygand procedure[6] exhibits a rotation of $[\alpha]_D^{22} = -16.5°$ ($c = 2$, methanol). Using the same starting materials, synthesis in water led to product *(5)* having $[\alpha]_D^{22} = -16.9°$ ($c = 2$, methanol). The coupling process in aqueous solution accordingly appears to be just as effective as proven techniques in organic phase. The pronounced acid-stability of the Peoc protecting groups[4a] permits simple deprotection of the Peoc-dipeptide esters. Thus the Peoc-dipeptide *(8)* could be obtained quantitatively from *(5)* by treatment with trifluoroacetic acid at room temperature for 2 h.



(5)

[$MePh_2$]Peoc-Leu-Phe-OH *(8)*

This *N*-protected peptide of two hydrophobic amino acids is adequately soluble in water containing 5% of methanol for further reactions, *e.g.*

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$$(8) + \text{H–Phe–O}t\text{Bu} \xrightarrow[H_2O]{(2),\,(3)} [\text{MePh}_2]\text{Peoc–Leu–Phe–Phe–O}t\text{Bu}$$

(9) 92%

In keeping with its phosphonium salt character, the Peoc-tripeptide ester *(9)* can be recrystallized like *(5)*, *(6)*, and *(7)* from dichloromethane/ether.

Procedure

To a stirred sample of the amino ester (2.5 mmol, or equivalent amounts of its toluenesulfonate and triethylamine) in water (10 ml) are added 1-hydroxybenzotriazole (0.34 g, 2.5 mmol) and, at 0°C, *N*-cyclohexyl-*N'*-β-(*N*-methylmorpholino)ethylcarbodiimide *p*-toluenesulfonate (1.2 g, 2.8 mmol; *ex* Merck) and Peoc-amino acid (2.5 mmol)[4]. After addition of water (10 ml) and cessation of cooling the suspension gradually clears and the Peoc-dipeptide ester precipitates as oil which is extracted after 48 h with CH_2Cl_2. The solution is washed with 1 N hydrochloric acid and water and dried over sodium sulfate. The foamy amorphous Peoc-dipeptide ester remaining on evaporation of the solvent is shown by its IR and ^{1}H-NMR spectra to contain tosylate ions. It is stirred with a solution of NaI in acetone, the precipitated sodium salts are filtered off, the filtrate is evaporated to dryness and digested with CH_2Cl_2. After renewed filtration the Peoc-dipeptide ester is obtained as the amorphous iodide by evaporation (traces of *(3)* cannot be removed by recrystallization from chloroform/ether or acetone/ethyl acetate/ether).

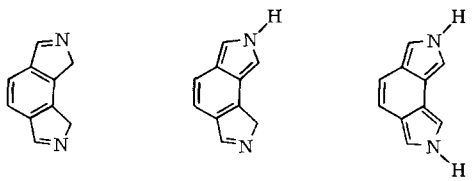
Received: September 13, 1977;
supplemented: October 12, 1977 [Z 870 IE]
German version: Angew. Chem. *90*, 63 (1978)

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Tricyclic Isoindoles[1]

By *Richard Kreher* and *Karl Josef Herd*[*]

The synthesis of the tricyclic hetarenes *(1)* was attempted in order to study the influence of annelation on the thermal stability and chemical reactivity of 1*H*- and 2*H*-isoindoles[3].



(1a) *(1b)* *(1c)*

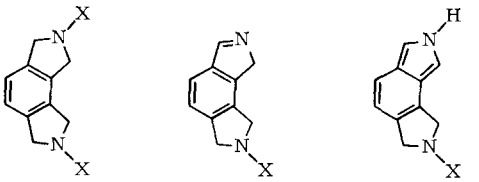
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We intended to establish, in the case of angular annelation, which of the tautomeric forms *(1a)*, *(1b)*, and *(1c)* with benzenoid or quinonoid structure is thermally more stable[4].

The synthetic goal was preparation of the benzenoid hetarene *(1a)* having two CN double bonds. With this aim 1,2,3,4-tetrakis(bromomethyl)benzene[5] was allowed to react with methanesulfonamide. The twofold cyclization was achieved in a one-step homogeneous reaction under basic conditions[2] (acetone/ethanol/water; 5 h/reflux), affording the desired product in 30% yield.

Introduction of the CN double bond[6] is accomplished by reaction of the tricyclic intermediate *(2)*, $X = SO_2CH_3$, m.p. >260°C, with potassium *tert*-butoxide in anhydrous dimethyl sulfoxide (2.5 h/65°C). 1,2-Elimination of methanesulfinic acid should then lead directly to the 1*H*-isoindole *(3a)*, which appears to rearrange into the tautomeric 2*H*-isoindole *(3c)* under basic reaction conditions. The NH group is established by an intense IR absorption band ($\nu = 3395\ cm^{-1}$) and by a broad ^{1}H-NMR signal ($\tau = -0.5$ to -2.5), which disappears by H/D exchange on addition of deuterium oxide. It follows from the NMR spectrum, as well as from the mass spectrum, that only one methylsulfonyl group is eliminated.

According to spectroscopic data the angular annelation of a heterocyclic five-membered ring does not lead to any change in stability[3]. The *o*-quinonoid structure *(3c)* is confirmed by chemical reaction with dienophiles (*N*-phenylmaleimide, dimethylacetylenedicarboxylate, and dimethyl azodicarboxylate)[7].



(2) *(3a)* *(3c)*

Table 1. 2-Methylsulfonyl-7*H*-1,3-dihydropyrrolo[3,4-*e*]isoindole *(3c)*.

$C_{10}H_9N_2X$, $X = SO_2CH_3$, yield 45—52%, m.p. 145—146°C (dec.) (ethyl acetate/*n*-heptane); ^{1}H-NMR (D_6-acetone + D_2O): $\tau = 2.46$ (dd, $J_{45} = 9$ Hz, $J_{56} = 0.5$ Hz, 1 H, CH-5), 2.64 (d, $J_{68} = 1.5$ Hz, 1 H, CH-8), 2.79 (mc, 1 H, CH-6), 3.24 (d, $J_{45} = 9$ Hz, 1 H, CH-4), 5.28 (s, broad, 2 H, CH_2), 5.33 (s, broad, 2 H, CH_2), 7.07 (s, 3 H, SO_2CH_3); UV (CH_2Cl_2, −20°C): λ_{max} ($\log\varepsilon$) = 265 (3.11), 281 (3.08), 291 (3.21), 313 (sh, 3.63), 325 (3.72), 337 (sh, 3.60) nm; MS (70 eV/160°C): *m/e* = 236 (16%, M^+), 157 (28%, $M^+ - SO_2CH_3$), 156 (100%, $M^+ - HO_2SCH_3$).

Table 2. 7*H*-Pyrrolo[3,4-*e*]isoindole *(1c)*.

$C_{10}H_8N_2$, yield 34%, m.p. >120°C (dec.), sublimation at 112—117°C/0.01 torr; ^{1}H-NMR (D_6-acetone + D_2O): $\tau = 2.80$ (d, $J_{13} = 2$ Hz, 2 H, CH-1 and CH-8), 2.95 (d, $J_{13} = 2$ Hz, 2 H, CH-3 and CH-6), 3.07 (s, 2 H, CH-4 and CH-5); ^{13}C-NMR (D_6-DMSO): $\delta = 120.0$ (int. 79, q), 115.7 (54, q), 115.1 (204), 110.6 (144), 107.2 (168); UV (CH_2Cl_2): λ_{max} ($\log\varepsilon$) = 257 (4.17), 261 (4.18), 273 (4.10), 290 (4.07), 300 (4.03), 327 (sh, 2.67) nm; MS (70 eV/110°C): *m/e* = 156 (100%, M^+), 152 (3%, $M^+ - 2H_2$).

The introduction of two CN double bonds in the same manner is possible in a one-step procedure under drastic conditions (3 h/110°C) starting from *(2)*. The twofold elimination of methanesulfinic acid can proceed in different directions leading to tautomeric 1*H*-isoindole *(1a)* or 2*H*-isoindole *(1b)* with the CN double bond in the 2,3- and/or 6,7-position, respectively. This phenomenon does not need further investigation, since the 1,2-elimination is accompanied by a spon-

taneous tautomeric rearrangement to the 7*H*-pyrrolo[3,4-*e*]-isoindole *(1c)*. The symmetrical molecular structure follows, mainly from the ^{1}H-NMR spectrum, which provides no evidence for tautomeric forms having a cyclic methylene group. The intense band at 3380 cm^{-1} in the IR spectrum is typical for the NH group, which gives rise to a broad signal ($\tau = -0.5$ to -1.5) in the ^{1}H-NMR spectrum. On addition of deuterium oxide in acetone or dimethyl sulfoxide a regiospecific H/D exchange takes place at the heteroatom.

The synthesis of the tricyclic hetarene *(1c)* provides evidence for the thermal stabilization of the 2*H*-isoindole by annelation of a pyrroloid ring system[8]. The chemical reactivity resembles that of 2*H*-isoindole, as exemplified by the sensitivity towards oxygen and the formation of a 1:2 adduct with *N*-phenylmaleimide. The structurally isomeric tricyclic hetarene with linear annelation might also be accessible by the same synthetic principle.

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CAS Registry numbers:
(1c), 65138-41-2; *(2)*, 65138-42-3; *(3c)*, 65138-43-4

[1] Studies on the Chemistry of Isoindoles and Isoindolenines, Part 13. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 12: [2].
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Molecular Structure of F_5SOSF_5, $F_5SeOSeF_5$, and $F_5TeOTeF_5$: d-Orbital Participation in Bonds between Main Group Elements[**]

By *Heinz Oberhammer* and *Konrad Seppelt*[*]

Do the bonding molecular orbitals in compounds of main group elements contain significant contributions from d atomic orbitals? Such d-orbital participation should be especially favored in SF_6, SeF_6, and TeF_6, owing to the number and the electronegativity of the fluorine atoms[1]. Recent SCF calculations (Xα-SW method) suggest a modest bonding contribution from chalcogen d orbitals[2], mainly as (pd)σ-bond ($2e_g$ orbital in SF_6) and more weakly as (pd)π bond ($1t_{2g}$ orbital). The older concept of "back donation" adequately describes the situation since the use of sulfur d orbitals does lead to a calculable drop in polarity of the bond.

In order to obtain experimental evidence for d-orbital participation, we have prepared the homologous chalcogen oxyfluorides F_5SOSeF_5, $F_5SeOSeF_5$, and $F_5TeOTeF_5$ by modified existing methods or by new ones, subjected them to rigorous purification, and investigated their structure by electron diffraction.

$$2SF_4 + OF_2 \xrightarrow{h\nu,\ -78\,^\circ C} F_5S{-}O{-}SF_5;\ \text{yield of pure cpd } 20\%$$

$$Xe(OSeF_5)_2 \xrightarrow{130\,^\circ C} F_5Se{-}O{-}SeF_5{}^{[3]};\ \text{yield of pure cpd } 18\%$$

$$TeO_2 + F_2/N_2 \longrightarrow F_5Te{-}O{-}TeF_5{}^{[4]};\ \text{yield of pure cpd } 12\%$$

All three compounds are exceptionally stable and have a relatively high vapor pressure at room temperature. The results

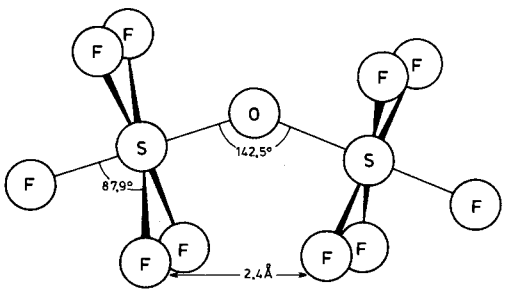


Fig. 1. Molecular structure of F_5SOSF_5.

Table 1. Bond lengths [Å] and bond angles [°] in the compounds $F_5X{-}O{-}XF_5$ [a].

	F_5SOSF_5	$F_5SeOSeF_5$	$F_5TeOTeF_5$	SF_6 [6]	SeF_6 [6]	TeF_6 [7]
X—O	1.586(11)	1.697(13)	1.832(12)			
X—F_m	1.560(4)	1.681(3)	1.816(4)	1.565	1.689	1.815(4)
X—F_e	1.558(8)	1.683(9)	1.820(10)			
X—F_a	1.572(34)	1.665(31)	1.799(47)			
∢ XOX	142.5(1.6)	142.4(1.9)	145.5(2.1)			
∢ F_aXF_e	87.9(0.9)	88.9(0.8)	89.8(0.9)			

[a] m, average; e, equatorial; a, axial.

The molecular structures show two unexpected features: a) the bond angle of the oxygen bridge is remarkably constant and large (142.5, 142.4, 145.5°). Purely steric considerations would suggest the angle to be largest in the sulfur compound because of the hindrance of four equatorial fluorine atoms. And in the tellurium compound, where the angle could be the smallest, it even increases slightly.—b) The two mutually hindering pairs of fluorine atoms are in an eclipsed arrangement although just a slight twisting of the XF_5 groups would considerably reduce the strain. (Due to the significance of this argument all three molecules were closely scrutinized for possible dihedral angles.) The deviation of the fluorine atoms by 2.1° from perfect octahedral geometry in the case of the sulfur

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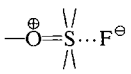
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

compound (by only 1.1° in $F_5SeOSeF_5$, and by 0.2° in $F_5TeOTeF_5$) points to the steric strain arising from this conformation.

The large and nearly constant bond angle and the eclipsed geometry suggest π-double bond contributions between the oxygen and the higher chalcogens. The X—O bonds are shorter than known single bond lengths and in the case of $F_5TeOTeF_5$ are equal to the formal double bond in gaseous TeO_2 (1.83 Å)[5]. This double bond is best characterized as an additional (pd)π bond to which d orbitals of d_{xy} type, *etc.*, contribute for reasons of symmetry—as described for SF_6 by the $1t_{2g}$ orbital. It may also be assumed that a (pd)π component of this kind is present in the chalcogen-fluorine bond of F_5XOXF_5 and XF_6 but is not experimentally detectable.

As indicated by the slightly increased bond angle and most drastically shortened bond, the (pd)π bonding contribution seems to be greatest in the tellurium compound.

The explanation using some (pd)π bonding can only be avoided by suggesting partial chalcogen-oxygen double bonds at the expense of chalcogen-fluorine bonds, in the manner of a hyperconjugation:



However, since the chalcogen-fluorine bonds are the same as those of the corresponding hexafluorides (cf. Table 1), this alternative can be ruled out. Ionic bonding contributions of the $^{\ominus}O—S^{\oplus}$ type (Schomaker-Stevenson relation) also fail to provide a satisfactory explanation because the difference in electronegativity is small.

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CAS Registry numbers:
$F_5S—O—SF_5$, 42310-84-9; $F_5Se—O—SeF_5$, 17653-61-1; $F_5Te—O—TeF_5$, 20533-01-1; SF_4, 7783-60-0; $Xe(OSeF_5)_2$, 38344-58-0; TeO_2, 7446-07-3; OF_2, 7783-41-7

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[7] *G. Gunderson, K. Hedberg* in Landolt-Börnstein II, 7, p. 77. Springer-Verlag, Berlin 1976.

ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

A mechanism for the transport and reduction of nitrate is proposed by *R. G. Butz* and *W. A. Jackson*. A tetrahedral aggregate of four nitrate reductase molecules is anchored in the membrane in such a way that one monomer faces outwards and the other three face inwards towards the cytoplasm. As a result, the transport and reduction of a nitrate ion is accompanied by the transport of two additional nitrate ions. The nitrate reductase is closely coupled to an ATPase which can be activated by nitrate; ADP can thus inhibit nitrate reduction by occupying the adenylate binding site of the ATPase. An analogous system, consisting of nitrate reductase dimers with associated ATPase, is proposed for nitrate transport and reduction in some algae and chloroplasts. [A Mechanism for Nitrate Transport and Reduction. Phytochemistry *16*, 409—417 (1977); 119 references]

[Rd 978 IE]

The hormone-dependent lipase of adipose tissue is the subject of an article by *D. Steinberg* and *J. C. Khoo*. Recent studies have shown that this enzyme is functionally and immunochemically different from the lipoprotein lipase which is responsible for the uptake of plasma triglycerides. Furthermore, the latter enzyme is not influenced by the cyclic AMP dependent protein kinase, which does however activate the hydrolases of adipose tissue which degrade tri-, di-, and monoglycerides as well as cholesterol esters. This activation is reversible; it is abolished by a protein phosphatase from heart and liver. [Hormone-Sensitive Lipase of Adipose Tissue. Federation Proc. *36*, 1986—1990 (1977); 44 references]

[Rd 979 IE]

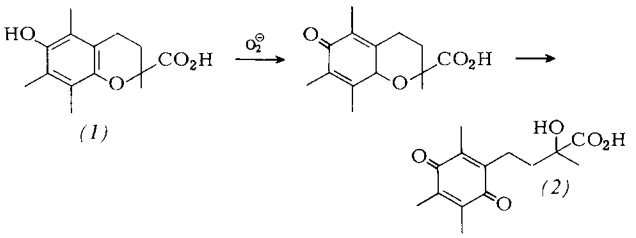
Uses of the trifluoromethanesulfonyl group in organic synthesis are outlined in an article by *J. B. Hendrickson, D. D. Sternbach*, and *K. K. Bair*. CF_3SO_2 ("trifyl") is reported to be one of the strongest electron-withdrawing groups known. All the properties (except nucleophilicity) which make the methanesulfonyl group especially valuable in synthetic organic chemistry are enhanced in CF_3SO_2. The primary electrophilic reagent is the anhydride, obtained from the acid by dehydration with P_2O_5. The most important nucleophilic form is the anion $CF_3SO_2^-$, obtained by reduction of the acid chloride with iodide. Both reagents are stable. In general, the CF_3SO_2 group is employed in the sense of a protecting group. It is inert to a wide variety of reaction conditions, but can be readily removed in various ways. [Trifyl Activation in Organic Synthesis. Acc. Chem. Res. *10*, 306—312 (1977); 44 references]

[Rd 989 IE]

Sulfilimines (sulfimides) are compounds of trivalent sulfur possessing a polar sulfur-nitrogen bond. Compared with the analogous sulfoxides they have been rather neglected, although they should be of similar chemical utility. A survey of the formation, stereochemistry, and reactions of sulfoxides and sulfilimines has been written by *S. Oae*. [Sulfoxides and Sulfilimines in *S. Oae*: Organic Chemistry of Sulfur. Plenum Press, New York 1977, pp. 383—471; 486 references]

[Rd 968 IE]

The organic chemistry of the hyperoxide ion (O_2^-) forms the theme of a progress report by *E. Lee-Ruff*. The hyperoxide ion is present in all aerobic organisms; its participation in biological oxidations has been investigated with the aid of simple model organic compounds. Thus, *e.g.*, the hydroxychroman *(1)* (vitamin E model) is transformed by O_2^- into the quinone *(2)*, which functions as a free radical scavenger;

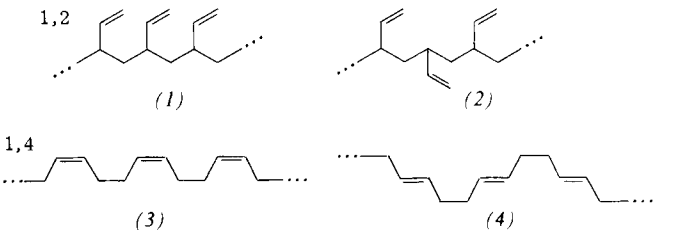


(1) *(2)*

similarly, vitamin E acts as an antioxidant for lipids. The reducing action of O_2^- was observed in its reaction with *o*- and *p*-benzoquinone, which are converted into the radical anions, while conversely the radical anion of 2,3-dimethylnaphthoquinone reduces O_2 to O_2^-. [The Organic Chemistry of Superoxides. Chem. Soc. Rev. *6*, 195—214 (1977); 145 references]

[Rd 986 IE]

The polymerization of butadiene is reviewed in an article by *D. H. Richards*. In principle the reaction can lead to four "homopolymers", all of which have been synthesized [*(1)* isotactic, *(2)* syndiotactic, *(3) cis*, and *(4) trans*]. Polybutadienes having a mixed structure (atactic) can be regarded as "copolymers". The structures have been investigated spectroscopically. The composition of the polymers largely depends upon the catalyst and the reaction conditions. Thus, radical-initiated emulsion polymerization leads to formation of a polymer containing 16—22% *(1)*+*(2)*, 3—20% *(3)* and 60—74% *(4)*; with titanium halogenides + AlR_3 or AlR_2X

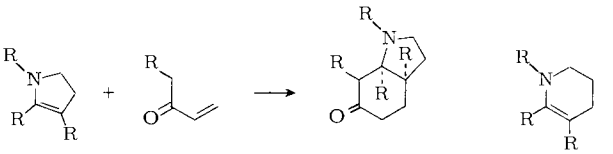


(1) *(2)* *(3)* *(4)*

up to 94% *(3)* is formed, with vanadium halogenides + AlR_3 or AlR_2X > 95% *(4)*. [The Polymerization and Copolymerization of Butadiene. Chem. Soc. Rev. *6*, 235—260 (1977); 114 references]

[Rd 987 IE]

General methods for the synthesis of alkaloids are reviewed by *R. V. Stevens*. In spite of the numerous different structures involved, it should be possible to generate a large number of the alkaloids from only two relatively simple synthons [*(1)* and *(4)*]. Reaction of *(1)* and *(4)*, respectively, with vinyl ketones such as *(2)* should afford hydrogenated indo-



(1) *(2)* *(3)* *(4)*

lones *(2)* and hydrogenated quinolones. The concept, which was put to the test using *(1)* as example, did in fact prove true and has permitted the synthesis of many alkaloids. [General Methods of Alkaloid Synthesis. Acc. Chem. Res. *10*, 193—198 (1977); 35 references]

[Rd 988 IE]

BOOK REVIEWS

Die toxikologisch-chemische Analyse (Toxicological-Chemical Analysis). By *R. K. Müller*. Verlag Chemie GmbH, Weinheim—New York 1977. 1st edit., xvi, 604 pp., 40 figs., 29 tables, bound, DM 138.—.

The field of toxicological-chemical analysis has long suffered from the lack of a concise and systematic laboratory handbook. This gap has now been successfully filled by the editor and 20 coauthors, whose work has made concise information with reference to more detailed literature available to a wide circle of interested readers.

Besides the principles of toxicology and pathological anatomy of intoxications, the authors treat the organization aspects: preservation, packaging, registration, and protocol, which provide the beginner in particular with a good introduction into this field of work.

The chapter on "Methods of Toxicological-Chemical Analysis" deserves special attention. It gives not only the methods of isolation, extraction, and separation, but also indications that enable the applicability of the relevant methods to be assessed. All the modern methods, such as UV, visible, IR, MS, and NMR spectroscopy are discussed.

What makes this book particularly valuable in practice is the alphabetically arranged monograph section giving currently interesting compounds divided into medicinal preparations, addictive drugs, and plant-protection agents; each entry is provided with brief information on use, constitution, melting point, molecular weight, solubility, behavior in TLC and the LD_{50}.

These data are collected in the concluding tables that systematize detection of the poison and are supplemented by information about TLC systems and color reactions from chromatographic detection, and by numerical characteristics such as λ_{max}, $E^{1\%}_{1cm}$, main and subsidiary bands (IR), and the principal peak (MS) of the substances dealt with. This work ends with an extensive subject index.

Lj. Kraus [NB 394 IE]

Block Copolymers—Overview and Critical Survey. By *A. Noshay* and *J. E. McGrath*. Academic Press, Inc., New York 1977. 1st edit., xvi, 516 pp., bound, $ 45.00.

This book is a successful attempt to systematize and to review critically the literature on block copolymers, which

has grown so enormously particularly in the last decade. Even though the authors place more emphasis on academic publications than on patent literature, this appears justified by the generally more informative content of the scientific papers.

The first part of the book treats the following problems, generally in qualitative but didactically very apt manner: definition of block copolymers, syntheses, possibilities of structure elucidation, properties, and applications. Above all, it is made clear that the structures reproduced mainly require demanding syntheses and that it is difficult to correlate structure and properties without a knowledge of chemical history. In some cases one can only resort to speculation. Particular attention is of course paid to the occurrence of both elastic and thermoplastic properties in one polymer, and the interesting possible applications of block polymers are discussed (membranes, protection of surfaces, biomedical applications). It is clearly indicated that valuable progress in this area can be expected if the synthetic processes can be made economical (continuous, without a solvent) and, in particular, if the methods of characterization can be improved.

In Part 2 block copolymers are systematically classified by the structure of the compounds into AB (two-block), ABA (three-block), and $(AB)_n$ (multiblock copolymers). Here the treatment follows established practice, but in this case specially adapted to the components, dealing with problems of synthesis, methods for the elucidation of structure, morphology of the products, relations between structure and properties, and comparison of properties with those of statistical copolymers having the same molecular composition. Clear reaction schemes, comparative tables, and diagrams facilitate an approach to the problems. This book is excellently suited not only for the expert but also for the reader hoping for an introduction into the field of block copolymers, not least because the cited literature (*ca.* 2000 references) was collected from a very wide field.

Oskar Nuyken [NB 386 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Chemische Analyse. Basiswissen. By *H. A. Bartels.* Volume 190 of "Heidelberger Taschenbücher". Springer-Verlag, Berlin 1977. viii, 91 pp., paperback, DM 19.80.—ISBN 3-540-08321-9

Elektrolytgleichgewichte und Elektrochemie. By *E.-G. Jäger, K. Schöne,* and *G. Werner.* Fachstudium Chemie, Arbeitsbuch 5. Verlag Chemie, Weinheim 1977. 308 pp., paperback, DM 34.—.—ISBN 3-527-25703-9

Progress in Inorganic Chemistry, Vol. 23. Edited by *St. J. Lippard.* John Wiley & Sons, New York 1977. 394 pp., bound, $ 33.00.—ISBN 0-471-02186-5

Chemistry of Natural Protein Fibers. Edited by *R. S. Asquith.* Plenum Press, New York 1977. xx, 417 pp., bound, $ 42.00.—ISBN 0-306-30898-3

Chromenes, Chromanones, and Chromones. Edited by *G. P. Ellis.* From the series "The Chemistry of Heterocyclic Compounds". Edited by *A. Weissberger* and *E. C. Taylor.* John Wiley & Sons, London 1977. 1196 pp., bound, £ 75.00.—ISBN 0-471-38212-4

Advances in Organometallic Chemistry, Vol. 15. Edited by *F. G. A. Stone* and *R. West.* Academic Press, New York 1977. vii, 332 pp., bound, $ 33.00.—ISBN 0-12-031115-1

Chemische Lebensmittelkonservierung. Stoffe, Wirkungen, Methoden. By *E. Lück.* Springer-Verlag, Berlin 1977. xx, 280 pp., bound, DM 58.—.—ISBN 3-540-08184-4

Marine Natural Products Chemistry. Edited by *D. J. Faulkner* and *W. H. Fenical.* Vol. IV, 1 of the "NATO Conference Series". Plenum Press, New York 1977. xi, 433 pp., bound, $ 51.00.—ISBN 0-306-32921-2

Anatomie und Physiologie des Menschen (15 Lehrprogramme). Vol. 6: Das Atmungssystem. By *D. F. Culclasure.* Verlag Chemie, Weinheim 1977. xxii, 97 pp., paperback, DM 15.50.—ISBN 3-527-25735-7

Chromatographic Systems. Maintenance and Troubleshooting. By *J. Q. Walker, M. T. Jackson, Jr.,* and *J. B. Maynard.* Academic Press, New York 1977. 2nd Edit., xiii, 359 pp., bound, $ 14.50.—ISBN 0-12-732052-0

Metal Toxicity in Mammals. Vol. 1: Physiologic and Chemical Basis for Metal Toxicity. By *T. D. Luckey* and *B. Venugopal.* Plenum Press, New York 1977. x, 238 pp., bound, $ 33.00.—ISBN 0-306-37176-2

Energy and the Atmosphere. A Physical-Chemical Approach. By *I. M. Campbell.* John Wiley & Sons, London 1977. ix, 398 pp., bound, £ 14.50/paperback, £ 5.95.—ISBN 0-471-99482-0 (bound); 0-471-99481-2 (paperback)

Explosives—a concise handbook. By *R. Meyer.* Verlag Chemie, Weinheim 1977. 358 pp., bound, DM 66.—.—ISBN 3-527-25630-X

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Restriction Endonucleases

By Werner Arber[*]

Restriction endonucleases are enzymes commonly found in bacteria which can fragment DNA. Cleavage of the DNA molecule takes place after recognition of a nucleotide sequence which is specific for each restriction endonuclease. Some of the enzymes split the DNA within the recognition sequence. This property allows these enzymes to be used for the systematic fragmentation of DNA molecules in structural and functional analyses of genetic material. The biological function of restriction endonucleases could be to provide a sort of primitive immune system which enables the cells to destroy foreign genetic material. Methylation of nucleotides lying within the recognition sequence serves to protect the cell's own DNA from being degraded by its restriction endonucleases. Restriction endonucleases were discovered during the investigation of the restriction of viral growth observed on changing hosts.

1. Introduction

Endonucleases are enzymes which can split nucleic acid chain molecules into fragments. Depending on the enzyme under consideration, the nucleic acid is cleaved more or less randomly or at specific sites which are determined, for example, by the nucleotide sequence of the nucleic acid. In principle, the prolonged action of an enzyme of the former type results in extensive degradation of the nucleic acid to give relatively small oligonucleotides. In contrast, the endonucleases which act at specific sites on deoxyribonucleic acid (DNA) produce reproducible populations of fragments of specific lengths; the ends of each fragment are determined by the specific cleavage sites of the enzyme.

This rough classification is not sufficient for many of the endonucleases studied in the past few years. It has namely been shown that some enzymes cannot carry out their endonucleolytic functions in the native state; they require a preliminary activation in which interaction with a specific recognition sequence of the nucleic acid plays an important role. The recognition sequence generally seems to be defined by a sequence of four to perhaps twenty nucleotides in the nucleic acid. The nucleotides critical for recognition need not necessarily follow one another but may be separated by nucleotides which are not important for recognition.

The term "restriction endonucleases" groups together a large number of microbial enzymes which cleave DNA in a specific manner. The fact that the cleavage reaction depends upon the interaction of the enzyme with a specific recognition sequence is an important common feature of all restriction endonucleases so far studied. According to the enzyme under consideration, the cleavage of the nucleic acid following this activation occurs either at the recognition site itself, at a defined distance away from the recognition site or, finally, at a position relatively far away from the recognition site and which varies from case to case. However, before we discuss the characterization of these reactions in more detail, the following biological considerations should help to account for the name given to this family of enzymes.

2. Discovery of the Restriction and Modification Systems

Whilst investigating the host specificity of bacterial viruses at the beginning of the 1950's, several research workers observed that on changing hosts these viruses often did not multiply very well at first, but then adapted to the new host and as a result then grew uninhibited[1–4]. This adaptation—so-called host-controlled modification—is not, however, genet-

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ically stable, *i.e.* it does not involve selection of a mutant capable of reproduction. The specific modification of the virus for a given host is, on the contrary, lost on growth in another host so that on reinfection of the first host only a small fraction of the virus particles can continue to multiply. This phenomenon of strong retardation of viral growth by the host was called restriction. Figure 1 illustrates, by way of example, host-controlled restriction and modification of bacterial viruses.

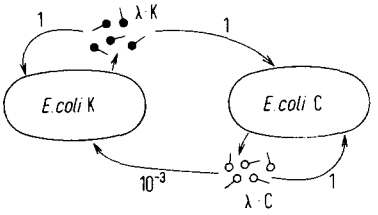


Fig. 1. Example of a restriction and modification system. The two *Escherichia coli* strains K and C are natural hosts for bacteriophage λ. As long as phage λ is grown on the same host, under optimal conditions each virus particle produces progeny viruses on infection (plating probability 1). On changing the host the following is observed: phage λ·C, which has grown on strain C, grows on strain K with a probability of only 10^{-3}. The few progeny particles are, however, now λ·K and thus grow well on strain K. On the other hand, λ·K also grows well on strain C but the newly produced viral progeny have now become λ·C and are no longer capable of infecting strain K. In this example strain K, but not strain C, possesses a restriction and modification system. C accepts all viruses, regardless of which host they have grown on. K only completely accepts those viruses which have previously grown on K and have thus been specifically modified for K. K modifies merely 1‰ of the viruses grown on C.

The molecular processes responsible for restriction and modification were largely elucidated at the beginning of the 1960's: both restriction and modification act directly on DNA, *i.e.* on the genetic material[5,6]. This was surprising, as it was known that the modification could not be further inherited in a genetically stable form. The following observations were crucial for the new findings: in the restriction situation (*e.g.* infection of strain K with phage λ·C, Fig. 1) the phage DNA was quickly degraded by the host cells which survived the infection. This meant that the genetic material foreign to the host cell was destroyed during restriction. If, on the other hand, the phage λ·K was allowed to multiply for a single growth cycle on a non-restrictive strain, then the only progeny to show K-specific modification (*i.e.* were capable of uninhibited infection of strain K) were those in which at least one of the two DNA strands consisted of parental material (semiconservative replication). This showed that the modification in strain K acted directly on the DNA and did not impede its further correct replication, and furthermore that the modifying principle remained associated with the parental DNA strand during replication.

It was then shown that the modification was due to the methylation of nucleotides[7-10]. In the example of strain K discussed here, certain adenine residues in specific nucleotide sequences are methylated to give N^6-methyladenine. This methylation does not change the genetic content of the nucleic acid in any way and seems to have the sole purpose of protecting the DNA against the action of the K-specific restriction endonuclease, the term now used for the DNA-degrading enzyme. This enzyme can, however, split all DNA molecules in which this specific methylation is lacking.

On the basis of these findings it is probable that restriction and modification systems are designed to defend their carrier cells against infection by foreign genetic material. The cell's own DNA is protected from the action of the restriction endonuclease by the modifying methylation. It soon became apparent that this phenomenon is not limited to viral DNA but also affects cellular DNA in the same way so that restriction is also effective, for example, in conjugation-mediated genetic exchange between two strains of bacteria[11-14].

Other biological functions than those discussed here, which are equivalent to those of a primitive immune system, have not so far been identified but discussions on this point have still not been concluded[15].

Restriction and modification systems have as yet only been detected unequivocally in bacteria. It seems that they are widely distributed in the large variety of bacterial species that exists. Systematic studies have so far been limited to a relatively small number of strains, above all to *Escherichia coli* and related enterobacteria, to *Bacillus subtilis* and various types of *Pseudomonas* and *Haemophilus*[16,17]. The genetic information for restriction and modification systems is often located in the bacterial chromosomes but occasionally also in plasmids or the genomes of bacteriophages. Natural strains of bacteria are found which have a single restriction and modification system, others have several, often unrelated systems and, finally, there are also strains in which restriction and modification systems have not as yet been detected. Mutants which no longer exhibit restriction and modification can also be isolated from strains with a restriction and modification system[18,19]. Under laboratory conditions these mutant strains do not seem to be at a disadvantage when compared with their unmutated parents, but this may not be the case in the ecological equilibrium of nature.

The effectiveness of a restriction and modification system with respect to a foreign genome depends, of course, on whether this genome is sensitive to the restriction and modification system under consideration. As has already been indicated, this requires the presence of specific recognition sites on the DNA molecule for the restriction and modification system. With very small DNA molecules (*e.g.* the genome of a small virus), it may be that no recognition site is to be found along the whole of the genome. If the genome contains, for example, a single recognition site, the sensitivity to the restriction is often lost due to mutation of a nucleotide at this specificity site[20]. In this way the recognition site can be genetically mapped. Historically speaking, this type of experiment led to appreciation of the fact that recognition sites play a key role in enzyme reactions[21].

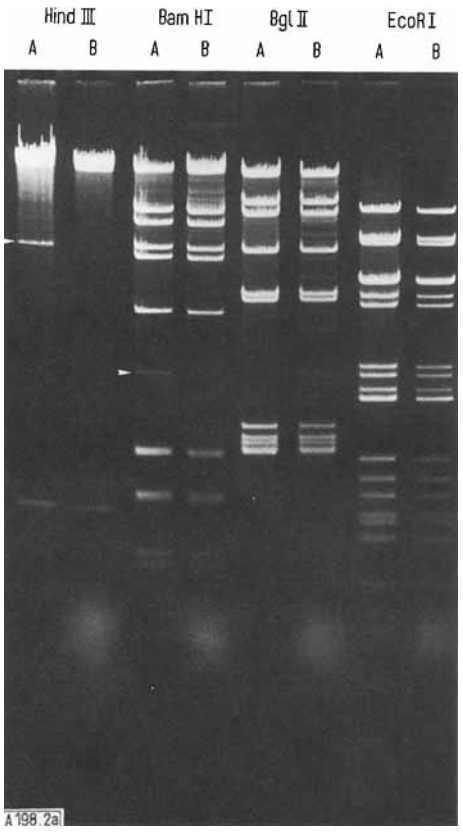
3. Enzymology of Restriction and Modification

After prolonged efforts, the restriction endonucleases from *E. coli* K and related strains were isolated towards the end of the 1960's[22-24]. It soon became clear that these rather large enzymes with molecular weights of approximately 450000 not only cleaved unmodified DNA *in vitro* but, under slightly modified reaction conditions, could also catalyze the specific methylation of the relevant restriction and modification system[25]. Each DNA strand received a methyl group

for each of its recognition sites[10]. It may be noted that, by definition, the methyl-accepting nucleotide is part of the recognition sequence, as completely methylated (*i. e.* modified) DNA is not attacked by the enzyme nor is the activity of the enzyme affected.

It was generally expected that the cleavage reaction would also occur at the recognition sites but this was not found to be the case. Rather, the cleavage products of the *in vitro* splitting of small DNA substrates having only a few recognition sites were shown to be of very variable sizes[26]. Thus, restriction cleavage brought about by restriction endonucleases from *E. coli* did not take place at the recognition site but at other positions on the DNA molecule and then not always at the same site. After cleavage of DNA with these enzymes, a given section (*e. g.* a specific gene) is not to be found in a uniform population of equally long fragments but, almost as is the case in random fragmentation, in fragments of very different lengths.

In 1970 it became clear that in this field nature also allows itself a variety of possibilities. Site-specific endonucleases were isolated from a strain of *Haemophilus influenzae*, and these enzymes were indeed able to split a given DNA substrate into a population of specific fragments[27]. Analysis of the nucleotide sequences at the ends of the cleavage products confirmed the specificity of the cleavage[28]. The present simplest test for demonstration of site-specific cleavage of a DNA molecule is the electrophoretic separation of the fragments in agarose gel[29]. The migration of the fragments in this medium is approximately inversely proportional to the logarithms of their molecular weights; the fragment bands are readily visible under UV light on addition of ethidium bromide (Fig. 2).



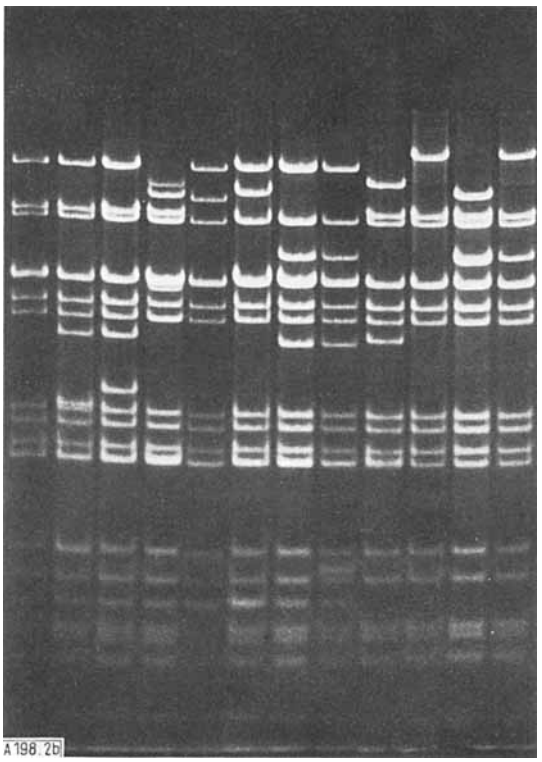


Fig. 2. Gel electrophoresis of restriction cleavage fragments of the bacteriophage P1 genome. a) Restriction cleavage of P1 DNA (A: isolated from phage particles; b: isolated as the prophage genome from P1 lysogenic bacteria) with the restriction endonucleases *Hind*III, *Bam*HI, *Bgl*II and *Eco*RI. The electrophoretic migration of the fragments in the agarose gel proceeds in the downward direction and is inversely proportional to the logarithm of the molecular weight. Large fragments are therefore at the top and small ones at the bottom. The fragments were visualized by addition of ethidium bromide and exposure to UV light. The bands marked with an arrowhead were only found in DNA extracted from phage particles; this indicates the specificity of the packaging of the DNA into phage particles (*Hind*III and *Bam*HI). All clearly visible bands are a result of complete digestion whereas weak bands originate from partial digestion (photograph: Dr. *Brigitte Bächi*). b) Comparison of the *Eco*RI fragmentation of P1 DNA (left slot) with that of eleven, independently isolated, deletion and insertion derivatives of bacteriophage P1. If the restriction cleavage map is known, the site of the deletion and insertion can be established from the missing bands. New bands originate from the region in which deletion has occurred, as well as from inserted material and its immediate vicinity. The six smallest *Eco*RI fragments of the P1 DNA have already moved out of the bottom of the gel (photograph: Dr. *Shigeru Iida*).

A few years ago a systematic search was begun for other such enzymes capable of site-specific cleavage of DNA molecules. Extracts from a large number of bacterial strains were intentionally purified crudely and examined, under relatively simply conceived, standard conditions, for their ability to specifically fragment several, selected DNA molecules. As expected, this procedure lead to the discovery of predominantly site-specific endonucleases whose isolation and detection was relatively unproblematic. The tests were probably unable to detect a series of similar enzymes which are less stable and are also dependent on cofactors. In spite of this, the investigations were surprisingly fruitful—to-date approximately 100 bacterial, site-specific endonucleases have already been described[17].

Only a few of these enzymes have so far been shown to belong to biologically characterized restriction and modification systems. It soon became customary, however, to refer to the whole group of described enzymes as "restriction endonucleases".

As has already been discussed, two vital components always belong to a restriction and modification system—namely the cleavage and the modification activities. It can well be assumed that modification is often brought about by means of methylation but other mechanisms for protecting the cell's own DNA from the restriction endonucleases can be envisaged.

4. Specific Recognition and Cleavage

As has already been described, relatively large enzyme complexes are found in *E. coli* bacteria which can either cleave or methylate DNA. It may be asked how these enzymes decide which function they should carry out. This decision seems to depend strongly on the primary structure of the DNA at the recognition sites. We now know that the restriction endonucleases from *E. coli* K can only recognize K-specific recognition sites effectively after activation with *S*-adenosylmethionine (Fig. 3). In double-stranded DNA such a site may be in one of the three following states: 1. It does not yet possess any methyl groups introduced by K-specific modification. This is normally the state of infective, foreign DNA. 2. One strand of the DNA is already methylated but not the other. This state is produced routinely after each replication cycle of previously completely modified DNA. 3. Both strands have a methyl group at the recognition site. This state is established shortly after DNA replication by the action of the modification activity on the second state.

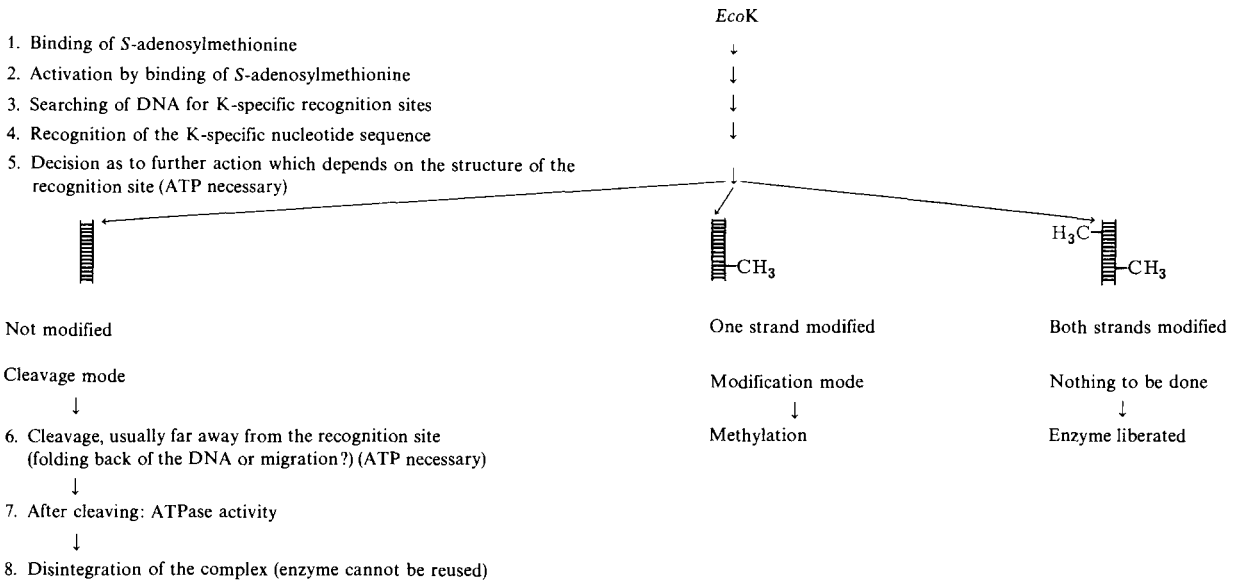


Fig. 3. Mode of action of the restriction endonuclease *Eco*K (schematic) [30, 31].

From the above it follows that it is to the cell's advantage if, in the case of unmodified (unmethylated) recognition sites, the enzyme complex decides in favor of cleaving the DNA which leads to the destruction of invading, foreign DNA; in the case of DNA modified (methylated) in one strand, it is better if the complex decides to methylate the second strand as well. Completely methylated recognition sites are also recognized by the enzyme, however these sites do not activate the enzyme but liberate it. This mode of action, which is logical for the cell, seems indeed to be the basis for the further behavior of the enzyme towards the DNA[32]. It is assumed that specific conformational changes occur as a physical manifestation of the decision taken in the recognition process; these changes direct the enzyme into either the cleavage or the methylation mode. It should be remembered that these complex *E. coli* enzymes cleave the DNA at a position far beyond the recognition site which could be achieved, for example, by folding back of the DNA molecule. At all events, ATP is required for cleavage as well as for active recognition.

One of the three gene products which constitute the enzyme complex seems to be primarily responsible for the actual recognition process of these enzymes[21]. Mutants of the gene responsible lose their capacity for specific recognition. The product of this gene couples the recognition specificity of the methylation reaction with that of the cleavage reaction. This situation points out the biological reason for the coupling of modification with restriction—the cell's own DNA has to be optimally protected.

The following picture can be drawn for at least some of the enzymes belonging to the large group of restriction endonucleases showing site-specific cleavage, but this should not however be generalized before more experimental data are available. The restriction endonuclease *Eco*RI coded for by an *E. coli* plasmid, is a dimer or tetramer of a polypeptide with a molecular weight of 28 500[33]. It is therefore the product of a single gene. This enzyme can only split DNA endonucleolytically but cannot protect against this cleavage. The same *E. coli* plasmid also codes, however, for a DNA methylase with a molecular weight of 40000[34, 35]. The methylation catalyzed by this enzyme occurs in the recognition sequence specific for the endonuclease *Eco*RI (Table 1). The two enzymes are thus the two parts of the *Eco*RI-specific restriction and modification system. In this case it should be noted that two, perhaps independent, gene products are involved which, under certain circumstances, could have been formed independently during evolution. This hypothesis has not however been proved experimentally; an initial gene duplication can also be envisaged which is followed by divergence of the two genes with retention of the part of the gene product necessary for specific recognition of a nucleotide sequence.

In some cases the endonucleolytic cleavage reaction has been studied more closely[22, 27, 33]. It was found that one of the strands of the double-stranded DNA is first split; under favorable conditions it is possible to isolate the resulting intermediate. The second DNA strand is also broken in a second step. A few restriction endonucleases also seem to be able to cleave single-stranded DNA specifically[36–38].

Analysis of the ends of the DNA fragments is of interest. The ends of the cleavage products of many restriction endonucleases cleaving at specific sites are very well characterized. Some of the enzymes split the two strands at the same level, others at positions some distance away from each other; in the latter case double-stranded DNA fragments are formed which have short, single-stranded ends. Table 1 contains some examples of both of these types. Where known, the position of the nucleotides which can be methylated in the modification reaction are also included in Table 1. Comparison of the examples shows the variety of possibilities which exist.

Table 1. Examples of recognition sequences of restriction endonucleases. Most of the data are taken from the publication of *Roberts* [17] which also contains the original references; the remaing data are the unpublished work of *R. J. Roberts* and *T. A. Bickle*. The recognition sequences are so arranged that their 5′ terminal ends are at the upper left and lower right hand sides. The cleavage sites are indicated by arrows. The nucleotides which are so far known to be methylated in the modification reaction are marked with an asterisk. Nucleotide bases: C = cytosine, G = guanine, A = adenine, T = thymine, Py = cytosine or thymine, Pu = guanine or adenine. The symbols for the restriction endonucleases were derived as follows: The first 3 letters give an abbreviation for the microorganism producing the enzyme, *e.g. Bam* for *Bacillus amyloliquefaciens*, the fourth letter (if any) designates the particular bacterial strain, the roman number given at the end identifies a particular enzyme isolated from the strain in question [47].

Recognition sequence	Specific for following restriction endonucleases
$G^{\downarrow}GATCC$ $CCTAG_{\uparrow}G$	*Bam*HI
$A^{\downarrow}GATCT$ $TCTAG_{\uparrow}A$	*Bgl*II
$^{\downarrow}G\overset{*}{A}TC$ $CTA\overset{*}{}G_{\uparrow}$	*Mbo*I
$\overset{*}{A}^{\downarrow}AGCTT$ $TTCGA_{\uparrow}\overset{*}{A}$	*Hin*dIII
$CTGCA^{\downarrow}G$ $G_{\uparrow}ACGTC$	*Pst*I
$G^{\downarrow}A\overset{*}{A}TTC$ $CTTA\overset{*}{}A_{\uparrow}G$	*Eco*RI
$GTPy^{\downarrow}Pu\overset{*}{A}C$ $CA\overset{*}{}Pu_{\uparrow}PyTG$	*Hin*dII
$^{\downarrow}C\overset{*}{C}AGG$ $GGTC\overset{*}{}C_{\uparrow}$	*Eco*RII
$C^{\downarrow}CCGGG$ $GGGCC_{\uparrow}C$	*Xma*I
$CCC^{\downarrow}GGG$ $GGG_{\uparrow}CCC$	*Sma*I
$C^{\downarrow}CGG$ $GGC_{\uparrow}C$	*Hpa*II, *Hap*II, *Mno*I
$TGG^{\downarrow}CCA$ $ACC_{\uparrow}GGT$	*Bal*I
$G G^{\downarrow} C C$ $C C_{\uparrow} G G$	*Bsu*I, *Hae*III

Almost all recognition sequences studied (see Table 1) exhibit twofold rotational symmetry. This may be connected with the specific interaction between the enzyme and double-stranded DNA. Knowledge of the number of nucleotide pairs comprising a recognition site, together with the fact that DNA is composed of only four nucleotides, allows prediction of the average frequency of a specific recognition sequence in the DNA. Similarly, the maximum possible number of recognition sequences of a given length can be calculated[21]. Seven of the 16 possible rotationally symmetrical tetranucleotide pairs have so far been demonstrated to be recognition sequences of one or more restriction endonucleases[17].

In this context it should be mentioned that two independent restriction endonucleases sometimes recognize the same nucleotide sequence but they then cleave in different ways. On the other hand, independent enzymes exist which produce the same cleavage products but which show marked differences in their enzyme kinetics[17].

5. Restriction Endonucleases in Biological Research

With the site-specifically cleaving restriction endonucleases nature has provided the research worker with a supply of long desired tools which allow genetic material to be systematically investigated. As long as the research worker had to rely on the occurrence of random breaks during the fragmentation of large DNA molecules, he could not expect to obtain uniform material for structural and functional analyses. This objective has meanwhile been attained with the restriction endonucleases.

One of the goals of the molecular geneticist is to identify the exact nucleotide sequence of a genome. As most gene carriers are very long DNA molecular chains, this problem must be approached systematically. Small genomes (*e.g.* the DNA molecules of small viruses) can be most easily analyzed. The first step of their analysis consists in drawing up a restriction cleavage map, *i.e.* one attempts to map all the cleavage sites of the genome which are specific for one or more restriction endonucleases (cf. Fig. 4). This can be achieved, for example, by a stepwise procedure involving isolation of partially cleaved intermediates or by double digestion experiments in which the cleavage products of one restriction endonuclease are isolated and then treated with a second restriction endonuclease. These, together with a series of supplementary techniques involving specific, radioactive-labeling of fragment ends, usually allow unequivocal physical genome maps to be constructed. An example is given in Figure 4.

The actual physical distances can be checked and uncertainties resolved by electron-microscopical studies involving hybridization between denatured restriction fragments themselves and between these fragments and the whole genome.

A further step consists in identifying the genetic information on sections of the genome. Here purified restriction fragments also play an important role, several routes may be tried to express the genetic information.

A series of very good methods is now available for determining the nucleotide sequence of DNA[41–43]. The ideal starting material is still however a preparation of the material to be analyzed which is as pure as possible. Fragments containing

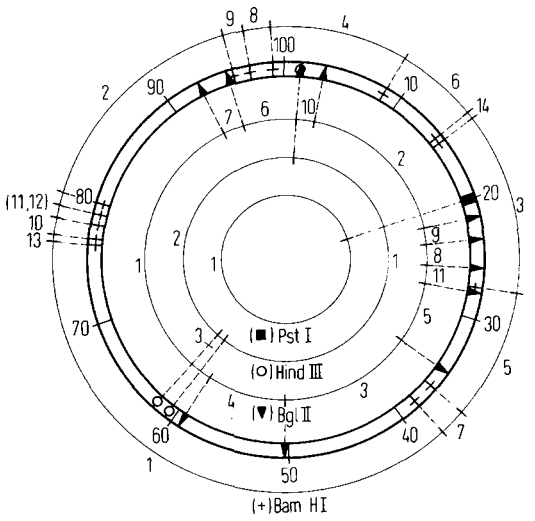


Fig. 4. Restriction cleavage map of the bacteriophage P1 genome [39]. The genome of bacteriophage P1 occurs as an autonomic plasmid in P1 lysogenic bacteria in the form of a circular DNA molecule with approximately 90000 base pairs (molecular weight approximately 59×10^6). For the physical genetic map the genome is subdivided into 100 units which are drawn to scale on the thickened circle. The cleavage sites of the four restriction endonucleases—*Pst*I (■), *Hind*III (○), *Bgl*II (▼) and *Bam*HI (+)—are also shown on this circle. The cleavage sites of each enzyme have been transferred to a separate, finely drawn ring; the DNA fragments are numbered according to their size (1 = longest fragment etc.). (The sequence of the neighboring fragments 11 and 12 arising from cleavage with *Bam*HI is not yet known.) As is shown in Table 1, each of the four restriction endonucleases utilized recognizes a specific sequence of six nucleotide pairs. In DNA which is statistically built up from the four natural deoxyribonucleotides (P1 DNA contains however approximately 23% guanine, 23% cytosine, 27% adenine and 27% thymine nucleotides [40]), one specific hexanucleotide can be statistically predicted for every 4096 nucleotides. For a DNA molecule the size of the P1 genome there would then be 22 recognition sites in each of the restriction endonucleases under consideration. Experimentally, eleven cleavage sites were found for *Bgl*II, 14 for *Bam*HI, three for *Hind*III and one for *Pst*I. On the other hand, the P1 genome has 26 cleavage sites for the enzyme *Eco*RI which also recognizes a specific hexanucleotide (Table 1). These data reflect the fact that the sequential arrangement of the nucleotide building blocks of the genetic material deviates from a purely statistical distribution.

approximately 100 nucleotides can be directly analyzed. With the help of detailed restriction cleavage maps, restriction endonucleases can be selected which permit a region of the genome to be cleaved into such fragments. It should perhaps be added that nowadays the primary interest of the molecular geneticist are the "punctuation marks" contained within a genome rather than the complete sequence of a gene coding for a specific polypeptide. Punctuation marks are sites on the nucleic acid at which, for example, mRNA replication or synthesis of a polypeptide begins and ends and also the sites which are important for the replication of the DNA itself. Further interest is centered on the sites which have specific affinities for functionally important gene products (*e.g.* repressor molecules). Finally, a great deal of attention has also been given to the study of those sites within a genome which are responsible for a considerably enhanced probability of recombination. It is hoped that more exact statements can be made about the mechanisms for the regulation of gene expression and the level of stability of the genetic material when the structure of all these sites is known. This research cannot of course be restricted solely to biochemical-physical investigations but must be supplemented by systematic genetic studies—the characterization of specific mutants and the investigation of their effects. Such investigations are therefore a very extensive undertaking and can only be directly applied to a few, selected, intensively studied systems.

It is however also desirable to analyze certain sections of more complex genomes (*e.g.* eukaryotic chromosomes) in detail. Here the use of restriction endonucleases has also been of considerable help. With the aid of the enzyme DNA ligase, single restriction cleavage fragments can be covalently incorporated into small DNA molecules (plasmids or bacteriophage genomes) which are capable of self-replication and in this case are called vectors[44, 45]. This incorporation is particularly easy if both the vector DNA and the DNA fragment to be inserted have short, complementary single-stranded ends, as is the case with the products of many of the restriction endonucleases (Table 1). Such ends hybridize spontaneously

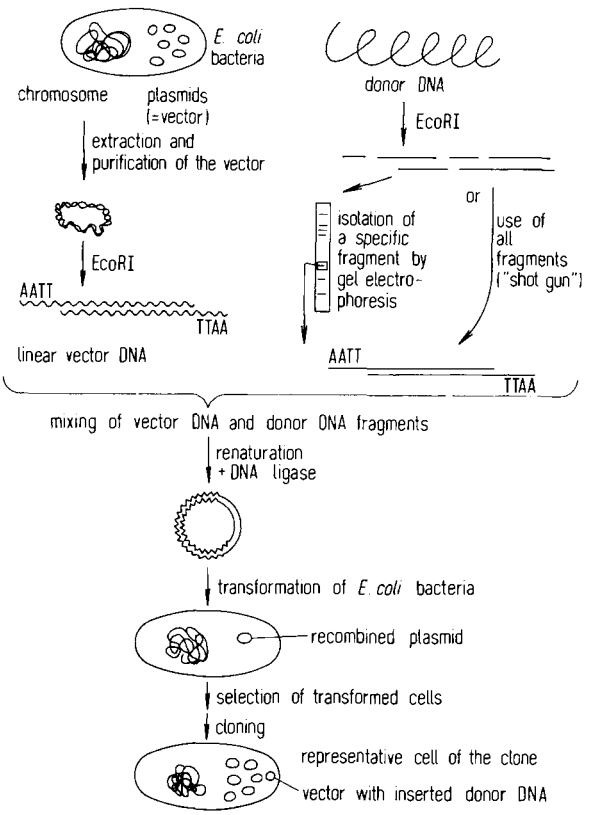


Fig. 5. Scheme for a simple *in vitro* recombination experiment. In the example illustrated here a small (molecular weight approximately 5×10^6), autonomically replicating plasmid serves as a vector; it only has a few well characterized genes and one cleavage site for *Eco*RI. On cleavage with *Eco*RI a linear DNA molecule with single-stranded ends is formed from the circular plasmid, these ends can easily recombine under renaturation conditions. If however donor DNA, which has likewise been cleaved with *Eco*RI, is added, one or more donor DNA fragments are then often incorporated into the ring which is formed. Cyclization to a covalently bound ring can be achieved by using the enzyme DNA ligase. In the transformation step the plasmid DNA penetrates an *E. coli* cell with a low but reproducible probability. The cells transformed with recombined plasmids can be selected from the large number of non-transformed *E. coli* cells by skilled choice of the vector based on the consideration of specific vector functions. The transformed bacteria are then purified by "cloning", *i.e.* by growing a culture from a single cell. All cells of a clone are therefore genetically and functionally identical. In the example given, each bacterial cell has several plasmids. Their numbers can be drastically increased by a special experimental procedure. The recombined donor DNA fragment can be obtained in its purified form and in the desired quantities by isolation of the recombined plasmids from the transformed clone and recleavage of the plasmid with *Eco*RI. The "clonable" donor DNA fragment may be several times larger than the plasmid. In principle no lower limit is set for this size. Before recombination a specific donor DNA fragment size can be selected by gel electrophoresis, alternatively all DNA fragments can be put into the renaturation mixture ("shot gun" experiment).

so that the DNA fragments brought together can be easily linked. This technique has become known as *in vitro* recombination of DNA (Fig. 5). It enables genetic material to combine whatever its origin. The aim of such experiments is to multiply the fragment inserted into the vector ("cloning") until there is sufficient material for structural and functional analyses. Such analyses could not of course be contemplated without thorough purification of the DNA segment of interest from the total gene carrier.

A further application of this technique consists in trying to express the known genetic information of a cloned DNA fragment under especially favorable conditions so that large quantities of this specific gene product are produced which can then be purified with relatively little difficulty. Possible applications of this method are, for example, the production of medically important antisera or other bioorganic gene products which are of ecological importance. In all these cases knowledge of the "punctuation marks" for optimal expression of the gene in question can play a significant role. There are still however many problems to be solved in this respect.

The possibility of *in vitro* combination of genetic material from different origins has confronted science with the question of the potential, scarcely predictable, undesirable effects of recombined gene material. Safety precautions for the prevention of possible risks have been proposed amazingly quickly[46]. How real the much discussed risks are can only be assessed when the gene flow within the total genetic potential is known. The question still to be answered is whether a certain amount of exchange of genetic information between unrelated living organisms is or was admissible during evolution and in daily biological events, or whether the barriers between species are very strict. There are indeed indications that a so-called, illegitimate exchange takes place repeatedly in nature, but concrete statistical data about this phenomenon are largely lacking and are also not easy to obtain. It can be asked whether the much discussed universality of the genetic code would also have come about if living organisms were forbidden to exchange sections of their genomes with unrelated species from time to time. With strict isolation one could imagine that more than one genetic code would have been formed.

As regards the world-wide discussion of the prohibition of certain lines of research which has been raised by the possibility of *in vitro* recombination of DNA, it may be apt to point out that, in every type of basic research, the long term effect of a result cannot be predicted. This makes control of research and the erection of barriers difficult. In about 1960 the investigation of the events in host-controlled restriction and modification of viruses was a purely microbiological problem with medical interest. One wanted to know how cells managed to ward off all viruses except those which had previously grown in their own sister cells. The finding that this repulsion took place at the level of the viral DNA and led to its degradation then opened up the way for the isolation of the restriction endonucleases and their further applications in the study of the structure and function of DNA.

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Use of Electron-Density Plots in Applied Quantum Chemistry

By Ilyas Absar and John R. Van Wazer[*]

The uses in applied quantum chemistry of computer-produced three-dimensional diagrams of electron-density distributions are discussed. The two major catagories of such diagrams are contrasted; and advantages are described for plots showing as the third dimension the point-by-point electron density in a cross-sectional cut (corresponding to the other two dimensions) through a molecule. Examples are presented to show how these plots may be used (1) to assess the adequacies of a given mathematical representation employed in the calculation of a wavefunction, (2) to clarify the interrelationship between an individual molecular orbital and the atomic orbitals of the constituent atoms, as well as (3) to explain the canonical set of molecular orbitals of any selected molecule. Furthermore these plots serve (4) to demonstrate clearly a replication of key characteristics between certain molecular orbitals in different molecules. These examples are accompanied by others which indicate how the electron-density plots may be used (5) to understand and clarify accepted chemical dogma. Finally, the possibility is discussed of employing quantum calculations on a wider scale so as to be of value in the more practical aspects of chemistry.

1. Introduction

Although electron-density diagrams have been used for many years in quantum chemistry, several kinds of three-dimensional plots accurately produced from wavefunctions by computer-controlled graphic systems have been introduced[1-4] since 1970. It has turned out that such plots are useful aids in interpreting[5] the results obtained from quantum calculations. Several books[5-7] treating this matter present many examples of such plots for various atoms and molecules; and it is our purpose here to survey these plots and to review some of their uses other than the obvious one of just depicting data.

2. Choice of Plots

Since a wavefunction, ψ, or its corresponding electron density, $\psi\psi^*$, must be described in four dimensions (three for the spatial geometry and one for the point-by-point value of the function), any three-dimensional plot must leave out some information; but yet no more than three dimensions may be depicted clearly in a spatial model or in its corresponding perspective diagram plotted on a sheet of paper. Two ways of handling this problem are commonly employed. One is to show the variation of the function across a chosen plane (or other surface) passing through the subject array of atoms, *e.g.* a molecule or crystal. In a linear or planar molecule, the chosen plane is generally selected to be that of the atoms; but, even for planar molecules, it is also often informative to plot one or more additional planes perpendicular to the plane of the molecule. For more complex molecular geometries, judicious selection of the planes to be studied must be made in order to depict clearly the spatial variation of the wavefunction or electron density. These cross-sectional plots have been prepared[6] using a linear or logarithmic scale for the electron density. Although the logarithmic scale (or a square-root or cube-root scale) has the advantage of encompassing the highest density values while simultaneously emphasizing the lower values appearing in the bonding and intermolecular regions, it does give a distorted density presentation. We prefer[5] to use a linear scale for the electron density and to truncate the sharp density peaks that appear close to the nuclei of atoms having core electrons.

The other way is to show only the surface(s) corresponding to some chosen value of the function in space so as to obtain what we usually call shape plots. The difficulties here are that the detailed spatial distribution of the function is thereby virtually ignored, while the selection of the chosen value of the function is extremely arbitrary. This latter problem is illustrated in Figure 1, in which a cross-sectional electron-density distribution (using a linear scale) for water sits on top of a series of shape plots corresponding to various chosen values of the electron density in this molecule. It is clear from these shape plots (a through e) that the choice of a relatively high electron density for this molecule will give only a tiny, nearly perfect sphere closely surrounding the oxygen nucleus; whereas a very low value will lead to a large, nearly spherical contour centered on the molecule. Thus, details of molecular structure will show up in shape plots only within a restricted intermediate range of the adjustable parameter (the chosen electron density). On those few occasions in which we find it valuable to calculate shape plots, we commonly employ a value for this parameter of $0.6\,e/Å^3$ for depicting the whole atom or molecule and $0.14\,e/Å^3$ for the constituent valence orbitals, since these choices were found[5] to correspond rather well to the van der Waals radii of common atoms from the second and third period of the Periodic Table. This choice of $0.14\,e/Å^3$ was employed in the shape plots describing the molecular orbitals of water[5] in Figure 2.

Because of the detailed point-by-point information presented in cross-sectional electron-density distributions, this

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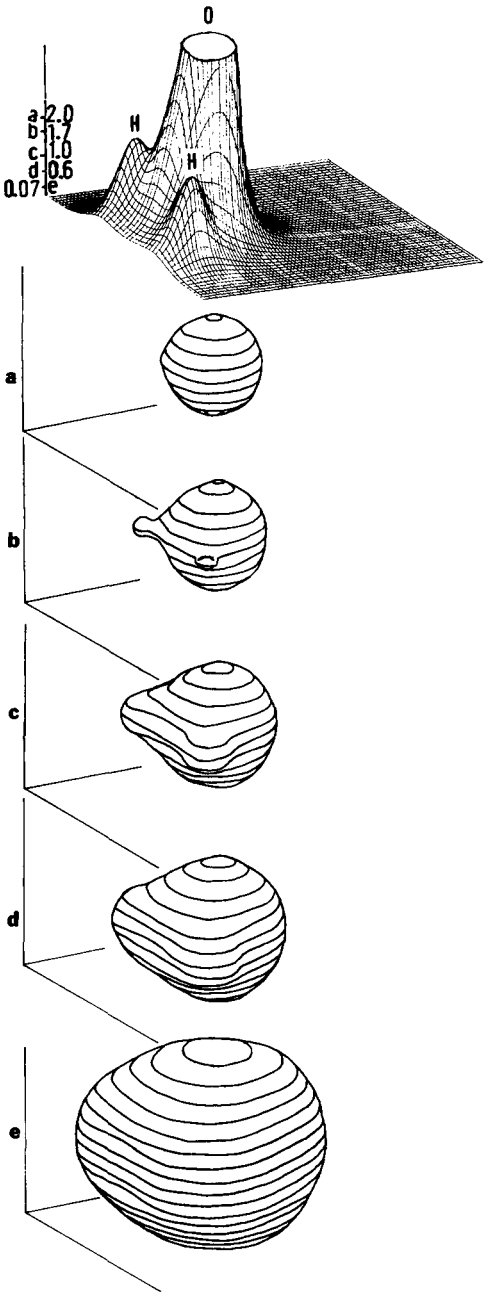


Fig. 1. Comparison of a cross-sectional electron-density plot (above) for the atomic plane of the water molecule with a series of shape plots. Shape plots a—e correspond to cuts through the cross-sectional diagram at the heights indicated.

kind of linearly scaled plot will be shown in most of the examples presented below to illustrate advantageous uses of the computer-produced three-dimensional graphs. Although it is possible to produce similar cross-sectional plots of wavefunctions ψ, we have decided not to include this approach among the following examples, since electron density $\psi\psi^*$ is a physically meaningful quantity while the wavefunction is not.

3. Adequacy of Various Mathematical Shortcuts

The usual off-hand criterion for the adequacy of a basis set employed in a self-consistent-field (SCF) calculation is the calculated total energy, with wavefunctions of higher quality giving lower (*i.e.* more negative) energies. This approach however may sometimes be misleading, so that a low-energy result can be of much poorer quality than one of appreciably higher energy. For example, we have intercompared[5] cross-sectional electron-density plots of the canonical molecular orbitals[*] of the water molecule calculated in a variety of basis sets. These plots showed, as expected, that an extended Slater[8] and a large Gaussian basis set[9] (both with polarizing functions) gave electronic distributions that were essentially identical and that the quality of much smaller Slater and Gaussian descriptions was quite good, except for a readily noted rounding of the top of the sharp humps corresponding to the hydrogen atoms in the Gaussian basis set. Indeed, even a CNDO semiempirical calculation[10, 11] gave quite well-shaped electronic distributions for each of the valence-shell molecular orbitals. However, as exemplified for orbital $1b_2$ in Figure 3, a one-center calculation[12] employing an extended-Slater basis set centered solely on the oxygen atom did very poorly in that there was no evidence whatsoever of the expected humps at the site of each hydrogen atom. This behavior was observed for all of the valence orbitals ($2a_1$, $1b_2$, and $3a_1$) that ought to show clumping of electronic charge around each hydrogen. It was also seen for the total electronic density.

The total energy was calculated to be -75.922 a.u. for this one-center representation as compared to -76.005 a.u. for the extended-Slater and only -75.703 a.u. for the minimum-Slater basis set[10] (which gave properly shaped electronic distributions). About 15 years ago, one-center calculations were very popular because (1) they were less costly than the usual calculation in which appropriate atomic orbitals were assigned to all of the atoms in the molecule and (2) the resulting total energies for a given level of adequacy of the basis set were very good for the molecules being studied at that time. On the basis of this one example, it would seem that the reason the one-center representation worked so well was that binary hydrides (such as methane, ammonia, and water) were emphasized in theoretical studies at that time. Because of the small energy contribution to a molecule from a hydrogen atom as compared to a second-period atom, a good basis set so improved the contribution of the latter to the total energy that neglect of the hydrogens was more than offset. Incidentally, most of the total energy of water is attributable to the presence of the oxygen core electrons. We suggest that anyone investigating an alternative method for calculating wavefunctions would be well advised to employ plots of the type described herein to see if the spatial distribution of the electron density (or the wavefunction) exhibits at least the proper gross shape.

During the last few years, one of us *(J. V. W.)* and his associates have been devoting considerable effort[13–15] to making the pseudopotential technique for solving the Schroedinger equation into a practical method (NOCOR) for use in everyday quantum chemistry. Therefore, quite early in this endeavor we compared cross-sectional electron-density plots of the valence shell for the NOCOR wavefunctions against those from an equivalent full-SCF calculation, as shown in

[*] The canonical molecular orbitals are understood to be that set among the infinite range of possible MOs which represents the solution of the Hartree-Fock SCF matrix and is adapted to the symmetry of the molecule. Cf. *W. Kutzelnigg*, Angew. Chem. *85*, 551 (1973); Angew. Chem. Int. Ed. Engl. *12*, 546 (1973), especially p. 559.

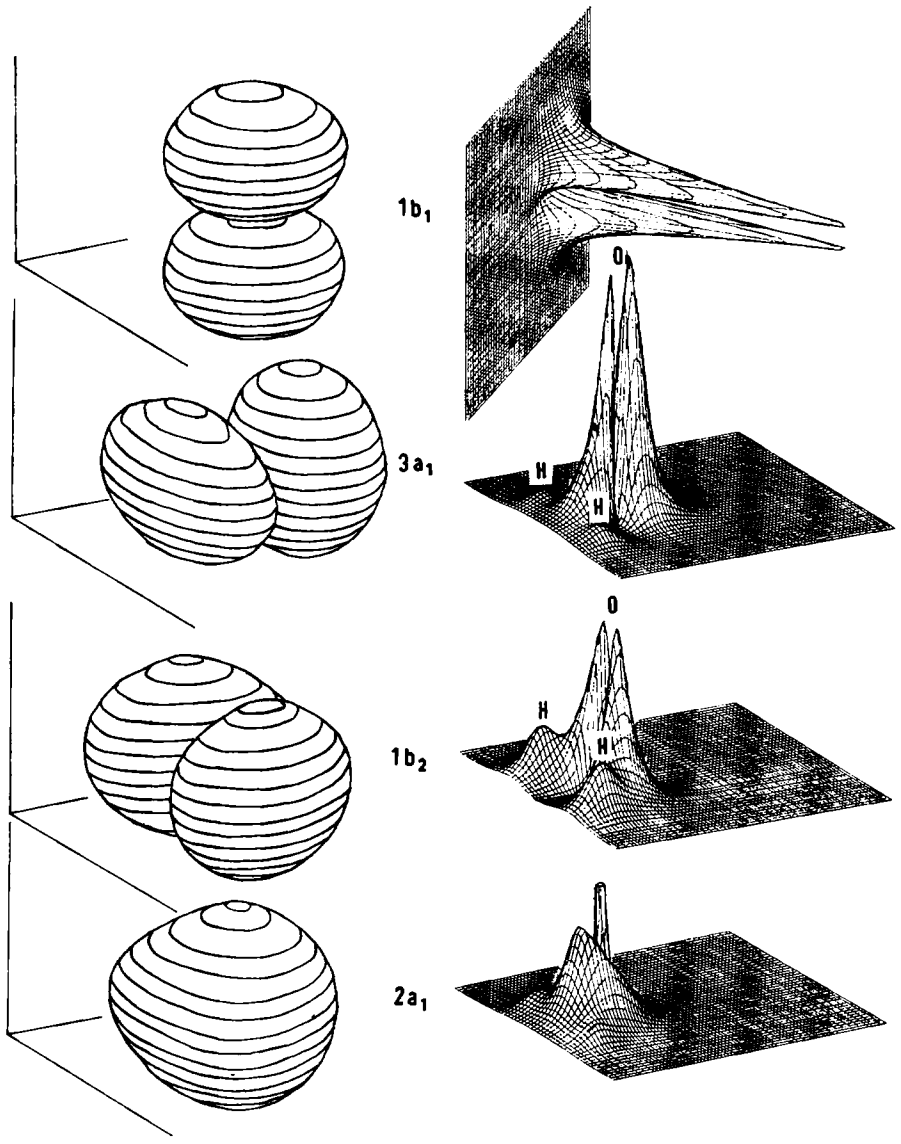


Fig. 2. Shape (left) and cross-sectional electron-density diagrams (right) for the valence-shell molecular orbitals of water.

Figure 4. In the usual NOCOR procedure, the valence electrons are handled by the standard SCF procedure while the set of core electrons of each atom are simulated by a potential function and the core-valence interactions are treated by the pseudopotential function V^{PP} [eq. 1], in which ε_c and ϕ_c represent the core eigenvalues and eigenfunctions, while the subscript v refers to a valence orbital and $\chi_v^{(i)}$ is a pseudo-wavefunction representing this valence orbital.

$$V^{PP}\chi_v^{(i)} = \sum_c |\phi_c\rangle (\varepsilon_v^{(i)} - \varepsilon_c) \langle \phi_c | \chi_v^{(i)} \rangle \qquad (1)$$

In view of the fact that in this approach there are no orthogonality restraints between the individual core electrons and a valence electron, the wavefunction of the latter has no need to exhibit a nodal structure in the core region. Therefore the electron densities corresponding to the valence molecular orbitals shown for the I_2 molecule[16] in Figure 4 smoothly die out in the core region in such a way that the integrated electronic density of each orbital in this region equals that corresponding to the summation of the antinodes occurring in the same region in the case of the same orbital obtained from a full-SCF calculation. The point of Figure 4 (and of similar intercomparisons of electron-density distribution plots from pseudopotential and full-SCF calculations) is that in the valence region the wavefunction of the total molecule or of each individual orbital is essentially indistinguishable from one obtained from an equivalent SCF calculation that includes all of the core electrons.

4. Interrelationships between Orbitals

Since atoms have only one nucleus, the symmetry of individual orbitals (*e.g.* s, p, d, *etc.*) must be discussed in terms of these orbitals and cannot be treated with respect to the nuclear geometry. On the other hand, it is standard practice in the case of molecular orbitals to employ appropriate group-theory designations derived from the symmetry of the nuclear arrangement (*e.g.* a_1, a_2, and e for a molecule of C_{3v} symmetry). As a result, this scheme of notation for describing molecular

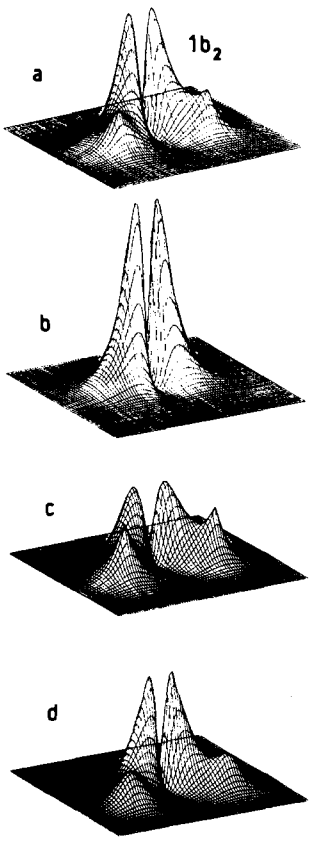


Fig. 3. Cross-sectional electron-density plots of the $1b_2$ orbital of water: a) with an extended-Slater basis set; b) in a one-center representation; c) in a minimum Slater presentation; d) with a moderately-sized Gaussian basis set employing seven s- and three p-type exponents for the oxygen and three s-type for each hydrogen.

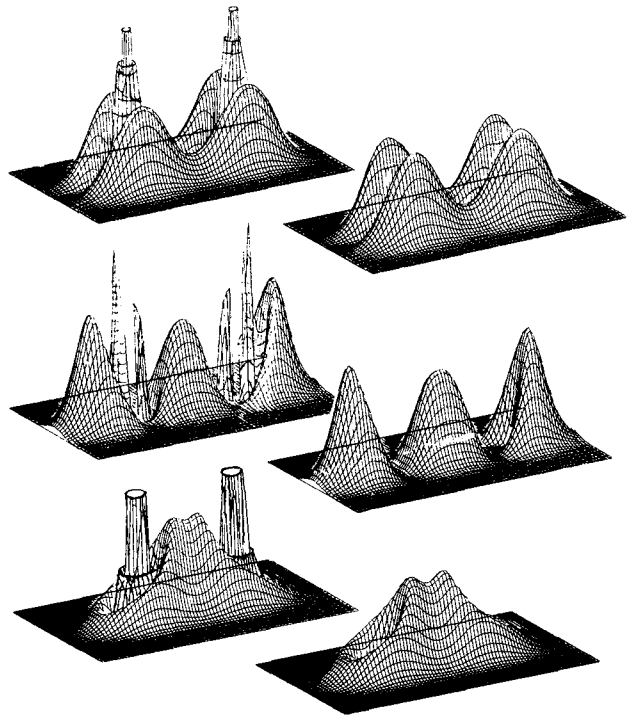


Fig. 4. Comparison of the electron-density plots of three valence orbitals (starting at the bottom, 19 σ_g, 21 σ_g, and 11 π_u) of the I_2 molecule as determined in a full-SCF calculation (left column) and by the NOCOR pseudopotential method (right column) in the same basis set. Note that the antinodes of the 5s and 5p contributing atomic orbitals appearing in the core region do not show up in the NOCOR calculation which, however, beautifully reproduces the valence-bonding structure.

orbitals does not make clear their constitution in terms of the atomic orbitals of the contributing atoms. However, the relationship between a molecular orbital and its contributing atomic orbitals may be seen at a glance from an electron-density distribution plot. The connection is clearly seen in either of the two kinds of plots shown in Figure 2, where the most stable of the H_2O valence orbitals, $2a_1$, is seen to be based on the 2s atomic orbital of oxygen. Each of the three remaining filled valence molecular orbitals of water is based on one of a set of three orthogonal oxygen p orbitals. The most stable of these three p-dominated orbitals is $1b_2$ in which the C_{2v} axis of the molecule passes through the nodal plane. This is followed by orbital $3a_1$ in which the nodal plane of the oxygen p orbital lies parallel to the line connecting the pair of hydrogen atoms. In the least stable of the filled orbitals, $1b_1$, the nodal plane passes through the two hydrogen atoms so that there can be no H—O bonding. As a result, when going from the most to the least stable of the valence orbitals, one proceeds from a nodeless molecular orbital through a set of three orbitals exhibiting orthogonal nodal planes—a molecular sequence that is reminiscent of the stability sequence found for a second-period isolated atom, *e.g.* 2s and the three 2p's. Moreover, atomic orbitals are utilized in building molecular orbitals in such a way that the more stable atomic orbitals appear in the more stable molecular orbitals as long as the nodal requirements of the orbitals are met. In other words, one can consider molecular orbitals in terms of a modified aufbau principle, that is analogous to the one concerned with atomic orbitals. This aufbau approach holds for the molecular orbitals of highly complicated molecules of varying symmetries, and this is readily seen[5] from the electron-density plots.

In working with electron-density plots of molecular orbitals, we noticed[17,18] that each molecular orbital of a given molecule bore striking resemblances (with respect to the magnitude and geometry of the individual atomic contributions) to molecular orbitals of other molecules. Even though this close correspondence between certain molecular orbitals in different molecules was sometimes seen in quite unrelated chemical structures, the effect was first noticed and is particularly pronounced in the case of a series of related molecules. This has been demonstrated in our orbital book[5] for a number of molecular sequences such as methanethiol, methanol, and dimethyl ether; methylamine, methylphosphane, and methylphosphorane; cyclopropane, phosphirane, and thiirane; or water, formaldehyde, and ketene. Most of the time, orbitals shown to be interrelated by inspection of the electron-density plots follow the standard orbital-correlation rules of quantum chemistry. However there are occasional exceptions, each of which may be explained logically.

As an example of these intermolecular relationships, consider the valence-shell molecular orbitals of H_2S, H_2SO, and H_2SO_2, the latter two molecules being analogs of sulfoxides and sulfones. The underlying computations on the progressive introduction of one and then two S—O bonds to H_2S have been reported[18]. Figure 5 shows the intermolecular relationships (dotted lines) between the molecular orbitals of H_2S, H_2SO, and H_2SO_2. Although most of these relationships can be established unambiguously from symmetry considerations, orbital-density plots not only give a clear-cut demonstration of which orbitals across a series of molecules are interrelated

but also delineate the details of how this occurs, thus leading to the resolution of any ambiguities.

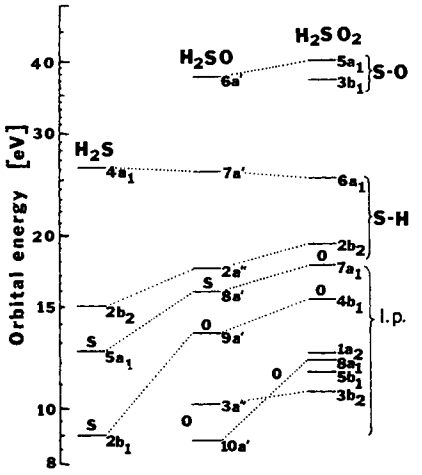


Fig. 5. A correlation plot for the valence orbitals of H_2S, H_2SO, and H_2SO_2, showing the most stable orbitals at the top. The orbitals involved in S—O and S—H bonding are so indicated; while l.p. stands for the lone-pair orbitals, with their assignment to either sulfur or oxygen being denoted above the line corresponding to each orbital.

Two orbital sequences involving shifts from sulfur lone-pair to oxygen lone-pair character are depicted in Figure 6. The sequence of Figure 6a ($5a_1$ of H_2S, 8a' of H_2SO, and $7a_1$ of H_2SO_2) shows a persistence of charge attributable to the sulfur lone pairs in H_2S, not only in H_2SO but also in H_2SO_2! It should be observed that the oxygen lone-pair charge in H_2SO reappears practically unchanged for each oxygen of H_2SO_2; also the small charge concentration lying on the axis between the two hydrogen atoms persists throughout the entire sequence. In Figure 6b are shown orbitals $2b_1$ of H_2S, 9a' of H_2SO, and $4b_1$ of H_2SO_2. The transition from sulfur to oxygen lone-pair character occurs through conversion of sulfur lone-pair charge into S—O bonding; however the character of the charge distribution about the sulfur nucleus again persists, the similarity being strikingly apparent in comparing the two more symmetric molecules H_2S and H_2SO_2.

5. Electron-Density Difference Plots

Variations in electron densities can be studied by the use of cross-sectional electron-density-difference plots, which are perhaps an even more powerful tool than the density plots themselves. Although the commonly used difference plots are those showing the electron density of the molecule minus the overlapping electron densities of the unbonded atoms positioned as in the molecule, difference plots may be used in many other ways, some quite novel.

An example of the common type of difference plot is shown according to our approach in Figure 7 for the ethane molecule, with the plane of observation passing through the two carbon atoms and a pair of *(anti)* hydrogen atoms[5]. Figure 7a depicts the electron density of the C_2H_6 molecule minus that due to superpositions of the two carbon atoms in their usual s^2p^2 ground state and the six hydrogen atoms, with these atoms centered at the proper positions corresponding to the ethane molecule and being described in the same basis set as the molecule. Figure 7b is a similar plot, except that in this case the carbon atoms have been hydridized to the sp^3 configuration. Both of these difference plots show an accumulation in the C—H and C—C bonding regions due to molecule formation. In Figure 7a the negative cones at the positions of the atomic nuclei clearly demonstrate that much of the change in charge between the atoms within and without the molecule involves the s orbitals of the carbon atoms. The major difference between the two plots is the sharp downward pointing peaks (Fig. 7a) and upward pointing peaks (Fig. 7b) at the carbon nuclei. This is due to the fact that, in the sp^3 hybridization of the carbon atoms, one of the 2s electrons of the s^2p^2 ground state was transferred to a 2p

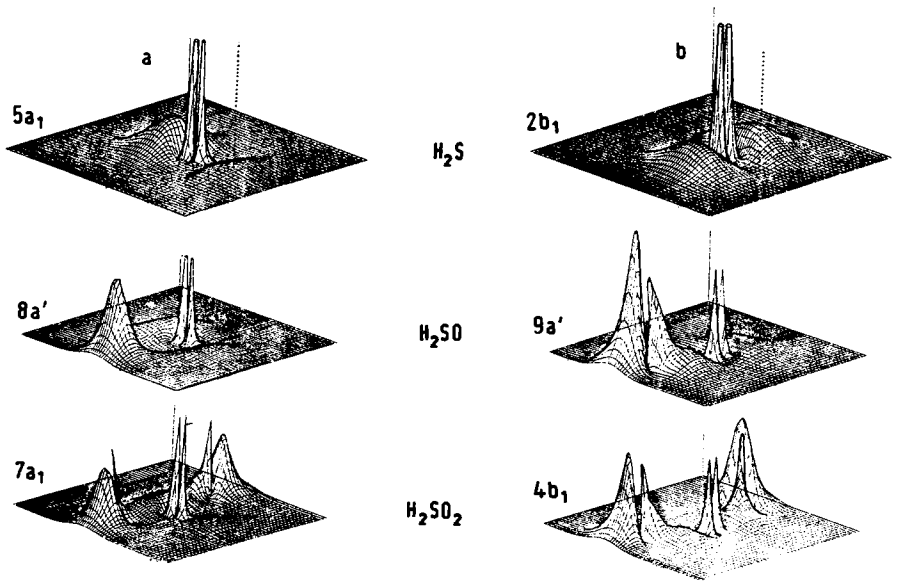


Fig. 6. Electron-density diagrams for two selected sets of correlated orbitals in the series of molecules: H_2S, H_2SO, and H_2SO_2. a) orbitals $5a_1$, 8a', $7a_1$; b) $2b_1$, 9a', $4b_1$.

orbital. The plots show that in the ground state there is too much whereas in the sp^3 hybrid there is not enough charge of the 2s type. Obviously, proper hybridization must lie somewhere in between.

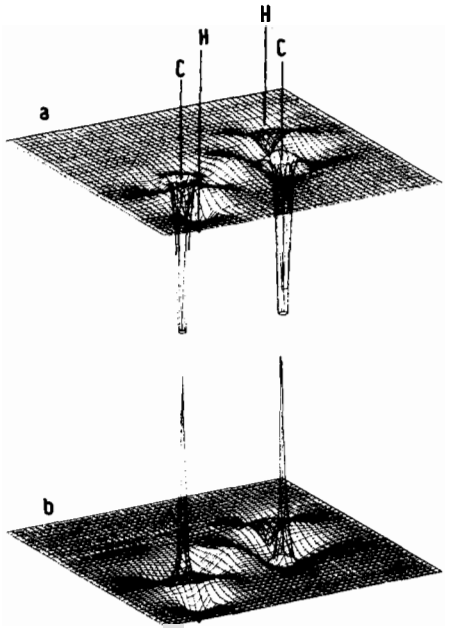


Fig. 7. Electron-density-difference plots for a plane passing through the two carbon atoms and a pair of *(anti)* hydrogen atoms in the ethane molecule. a) molecular electron density minus that obtained by summing over the ground-state constituent atoms placed in the same positions in which they appear in the molecule. b) as in a) except that the carbon atoms of the summation have been hybridized to the sp^3 configuration. These diagrams are plotted to show both plus and minus differences, so that they appear to be transparent. Note that the electron-density differences in these plots are magnified to show up details.

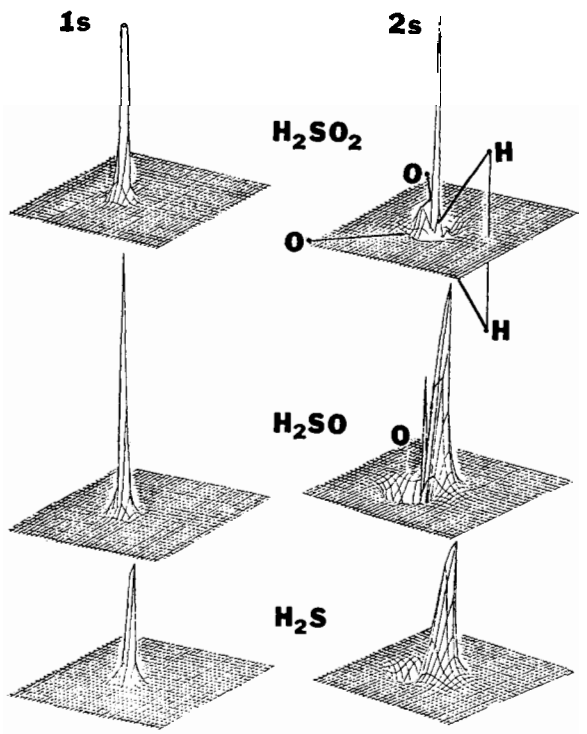


Fig. 8. Cross-sectional electron-density plots of the sulfur core orbitals of s symmetry in the series of molecules H_2S, H_2SO, and H_2SO_2. Note that the 2s orbital exhibits appreciable deformation from its spherical shape in the isolated sulfur atom; whereas this is not true for the 1s orbital. The positions of the hydrogen and oxygen atoms are indicated on one of these plots.

An example of the novel usage of electron-density-difference maps is to elucidate very small changes in electronic structure, as was found in a study[19] of the relationship between the inner-shell molecular orbitals of a series of structurally related molecules. Figure 8 shows electron-density-difference maps for the sulfur "1s" and "2s" molecular orbitals minus the respective atomic orbitals for H_2S, H_2SO, and H_2SO_2. Note that the charge distribution of the sulfur "2s" core electron in any of these molecules no longer exhibits spherical symmetry. This effect is most pronounced in the "2s" orbitals of H_2S and H_2SO, the two cases where sulfur lone pairs are present. Figure 8 demonstrates that the core electrons are not as insensitive to changes in the valence structure as was supposed for so many years. Inner-orbital photoelectron spectroscopy (ESCA) has experimentally demonstrated this fact with respect to the core binding energies[20–22]. The matter of small geometrical deformations in core orbitals (as indicated in Fig. 8) is worthy of further consideration in more precise calculations than the moderately sized basis sets we employed. Other interesting phenomena (such as the electronic effects of internal rotation about a particular bond, ring-closure reactions, and the significance of discussing particular bonds with respect to their covalent or ionic character) are fruitfully studied[5] using electron-density-difference plots. A set of difference plots showing the effect of allowing d character to third-period atoms in a molecule is presented in Figure 10 (see below).

6. Clarification of Chemical Dogma

There is a common misconception that SCF wavefunctions are too delocalized for direct interpretation. As a result, considerable effort has been put into schemes[23–26] for the localization of the canonical molecular orbitals resulting from single-determinant SCF calculations. However, one of the important contributions to the understanding of molecular orbitals made by electron-density plots is a clear demonstration of the fact that canonical molecular orbitals are readily understood in terms of the constituent atomic orbitals and that their interpretation in terms of standard chemical theory is easy and straightforward. This has been demonstrated by our book[5] and numerous papers from our group[2,17,18,27–31]. Although the numerical array of a wavefunction (or many of the various other mathematical arrays which can be used to represent it) may be utilized to characterize a molecular orbital with respect to the details of its atomic makeup, this approach is somewhat cumbersome and often not fully informative, even for those experienced in the mathematics of quantum chemistry. On the other hand, a quick visual inspection of a properly chosen three-dimensional cross-sectional electron-density plot shows up the details with great clarity.

The fact that a single-determinant wavefunction can be decomposed into an infinite number of different sets of "orbitals" has led some people to feel that molecular orbitals are highly arbitrary constructs. This is untrue however, since the molecular orbitals obtained from a standard SCF calculation (the canonical set) are just as meaningful as is the use of s, p, d, *etc.* orbitals for describing isolated atoms, and in the same sense. This means that anyone who uses the standard s-p-d nomenclature for describing the symmetry of atomic

orbitals must, for exactly the same reasons that these atomic orbitals were chosen over other alternatives (hybrids), put equal faith in the canonical molecular orbitals. Inspection of cross-sectional electron-density plots (*e.g.* see Figs. 2—9) shows how the canonical molecular orbitals retain much of the form of the constituent atomic orbitals.

The σ, π, and δ notation used in discussing chemical bonding properly applies only to linear molecules. However, for many years chemists have applied this notation to molecules having other than linear symmetry, sometimes quite inappropriately. Another aspect of three-dimension cross-sectional electron-density plots is that they show graphically how appropriate is the use of this notation for discussing chemical bonding in a given molecule and demonstrate the complications involved. For example, examination of a series of electron-density diagrams corresponding to varying amounts of internal rotation of a molecule which does not exhibit a high degree of symmetry with respect to the bond axis of rotation has shown that in such cases one can indeed speak of twisting of the electronic distributions making up the bond. This behavior is demonstrated by the valence orbitals of diphosphane. As shown in Figure 9, an H_2PPH_2 orbital[30] which is π-like with respect to the P—P bond in the eclipsed and staggered forms of diphosphane, may be considered as being a twisted π bond in the intermediate rotameric forms in which the pair of hydrogen atoms on each phosphorus are no longer present in relative positions which would allow "normal" π-bonding[5].

In discussing the contribution of d orbitals to the chemistry of atoms of the Third Period, chemists have customarily differentiated sharply between $p_\pi \rightarrow d_\pi$ charge transfer and the polarization of d orbitals. When electron-density plots are made for most molecules (even those in which $p_\pi \rightarrow d_\pi$ charge transfer is to be expected), it turns out that electron-density plots of the entire molecule, the valence shell, or, to a lesser extent, the various individual orbitals as calculated with d character being allowed or disallowed to the charge-accepting atom differ only slightly. However, by subtracting the point-by-point electron density in, say, the no-d plot from that in the plot where d character was incorporated, one obtains an electron-density-difference plot in which the only features are the small changes from the one to the other of the electron-density distributions being compared.

For example, in the case of the chlorosilane molecule, *Howell* and *Van Wazer* carried out four SCF calculations[31]: One corresponding to d orbitals being disallowed, another with appropriate d functions being incorporated into the mathematical description of the silicon atom, and a third with the d functions being alloted to the chlorine. The fourth case corresponded to d character being allowed to both the silicon and the chlorine atoms. The usual kind of numerical data reported from SCF calculations are presented for this molecule in Table 1, from which it should be noted that the greatest stabilization upon adding d character to the molecule results from placing the d function on the silicon rather than on the chlorine. This stabilization is reflected in both the Si—Cl and Si—H overlap charges. The Mulliken charge on the silicon atom is particularly affected by putting the d orbital on the silicon, going from the no-d value of +0.3 to −0.3 upon adding d character to the silicon in this basis set. These findings would customarily be interpreted to show that, upon allowing d character to the silicon, there is a large transfer of charge to that atom; whereas, when it is allowed to the

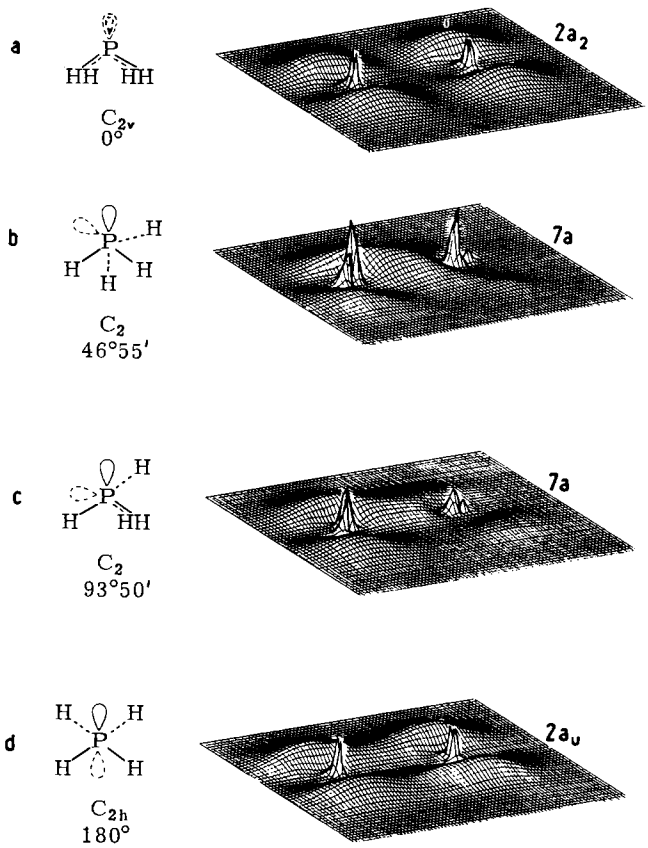


Fig. 9. Cross-sectional electron-density plots for one series of related orbitals obtained by internal rotation of the diphosphane molecule (H_2PPH_2). a) eclipsed; b) *gauche*; c) semieclipsed; d) staggered.

Table 1. Some properties calculated for chlorosilane (H_3SiCl).

Property	without d orbitals	with d orbitals for silicon	with d orbitals for chlorine	with d orbitals for silicon + chlorine
Total energy [a.u.]	−749.483	−749.577	−749.503	−749.589
Binding energy [a] [eV]	9.0	11.6	9.6	11.9
Charge on Si	+ 0.31	− 0.30	+ 0.41	− 0.21
Charge on Cl	− 0.12	+ 0.04	− 0.18	− 0.03
Charge on H	− 0.06	+ 0.09	− 0.08	+ 0.08
S-Cl overlap	0.61	0.86	0.65	0.89
S-H overlap	0.69	0.81	0.70	0.81

[a] The binding energy is the difference between the sum of the total energies of the constituent atoms and the total molecular energy, with 1 a.u. = 27.21 eV and no correction for electron correlation.

chlorine, the charge is transferred away from that atom. The casual interpretation is that the d orbitals on silicon are splendidly adapted to collecting charge; whereas d character on the chlorine leads to a small amount of charge loss, primarily to the hydrogen atoms. The standard code words for these observations are p→d transfer involving the silicon d orbitals and a simple polarizing effect (accompanied by little charge transfer) due to the chlorine d orbitals.

antibonding. Orbitals 3e and 4e are characterized by Si—Cl π bonding and antibonding, respectively. The data of this table also give support to the accepted picture of the effect of adding d character to either the silicon or the chlorine atom.

Figures 10a and 10b show electron-density-difference plots for the total molecule and for orbitals 9a and 4e. These orbitals were chosen because they exhibit a particularly large

Table 2. Interatomic charge transfer in each molecular orbital of chlorosilane (H_3SiCl) from adding d character.

Orbital	Predominant character	Charge transfer upon adding d to Si atom	Charge transfer upon adding d to Cl atom
4e	Cl $n_{\perp}$ + (Si—Cl)π^*	Cl $\xrightarrow{0.211}$ Si $\xrightarrow{0.116}$ 3H	3H $\xrightarrow{0.015}$ Si $\xrightarrow{0.014}$ Cl
9a	(Si—Cl)σ + Cl $n_{\parallel}$	Cl $\xrightarrow{0.033}$ Si $\xleftarrow{0.026}$ 3H	Cl $\xleftarrow{0.011}$ Si $\xrightarrow{0.007}$ 3H
3e	(Si—H)σ + (Si—Cl)π	3H $\xrightarrow{0.292}$ Si $\xrightarrow{0.084}$ Cl	Cl $\xrightarrow{0.005}$ Si $\xrightarrow{0.052}$ 3H
8a	(Si—H)σ + (Si—Cl)σ^*	Si $\xrightarrow{0.006}$ 3H	Cl $\xleftarrow{0.012}$ Si $\xrightarrow{0.003}$ 3H
7a	(Si—Cl)σ + Cl $n_{\parallel}$	Cl $\xrightarrow{0.006}$ Si $\xrightarrow{0.002}$ 3H	Si $\xrightarrow{0.022}$ Cl

In Table 2, the calculated interatomic charge transfer is shown for the individual H_3SiCl valence orbitals due to adding d character to either the silicon or the chlorine atom. Note that the second column of this table indicates the predominate character of each orbital with respect to the Si—Cl and Si—H bonds, as well as to the chlorine lone pairs. The lone pairs are indicated by the letter n followed by either a $\parallel$ or a $\perp$ sign to indicate that the lone-pair charge being discussed is disposed along the C_{3v} axis of the molecule or on either side of this axis respectively. The bonding character of each molecular orbital is readily seen in its electron-density plot, although some additional information can be obtained from the numerical data. Note in Table 2 that orbital 7a exhibits appreciable Si—Cl σ bonding, whereas 8a shows Si—Cl σ amount of charge transfer, according to either the full set of difference plots or the charge-transfer data of Table 2. In order to orient the reader, regular electron-density-distribution plots are presented in Figure 10c. These plots for the two selected molecular orbitals clearly demonstrate the π anti- or nonbonding character of orbital 4e with respect to the Si—Cl bond and the σ character of orbital 9a with respect to this bond.

It seems apparent from inspection of Figure 10 that allowing d character to either the chlorine or the silicon gives rather similar charge rearrangements; except for the fact that, when the d orbitals are on the silicon, the interaction between this atom and its neighboring hydrogens is also considerably modified. The net effect of adding d character to either the

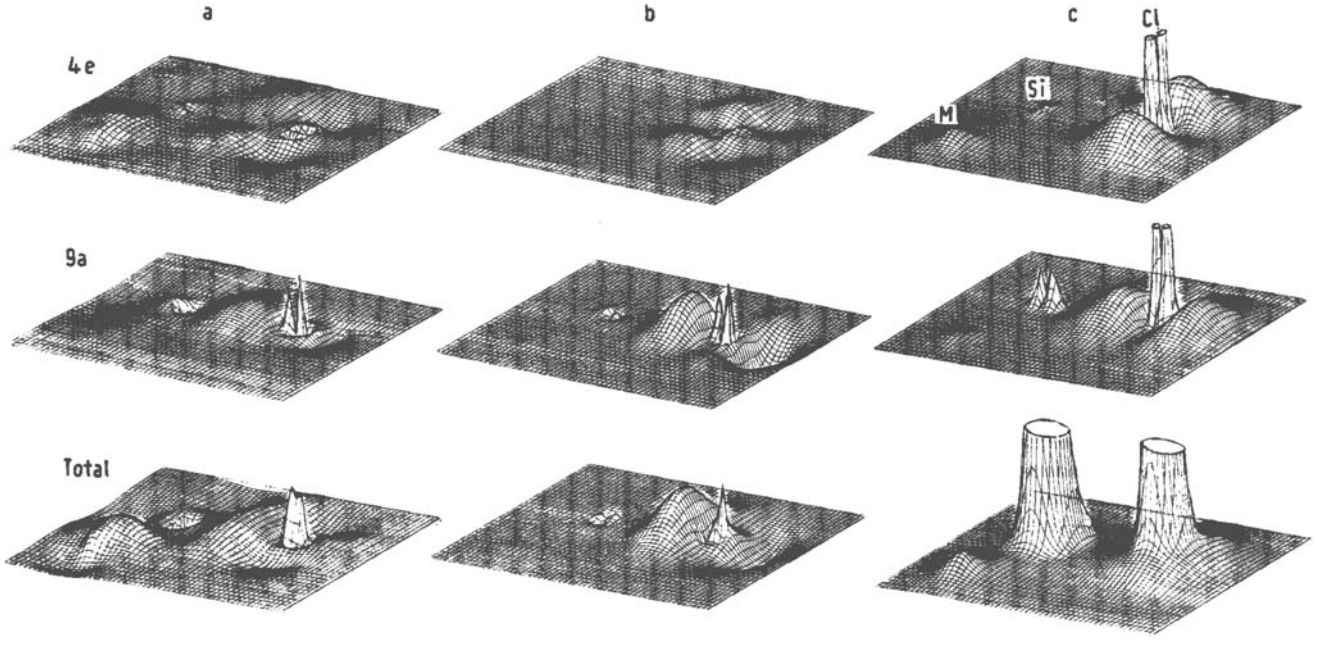


Fig. 10. Difference plots showing the effect of allowing d character to a) the silicon and b) the chlorine atoms in chlorosilane for two selected valence-shell orbitals and the total molecule. c) Cross-sectional electron-density plots at a fifth of the magnification employed in the difference plots (not including d orbitals). The molecule is so arranged that the reference plane passes through the silicon and chlorine atoms as well as one of the hydrogen atoms.

silicon or the chlorine is to move charge from the lone-pair region of the chlorine atom to the Si—Cl bonding region, and thereby to reduce the polarity of the molecule, as indicated by the respective calculated dipole moments. Therefore, it seems clear that the mathematical description of the H_3SiCl molecule in the limited (sp) basis set employed is constrained so that there is too much charge in the chlorine lone-pair region unless d functions are employed somewhere. The real purpose of supplementing a basis set with orbitals exhibiting more angular degrees of freedom is simply to lessen the constraints placed on the mathematical description so that shape of the electronic distribution will approach its optimum value. It is clear from the chlorosilane example discussed here that the language used to describe the charge shifts is in many respects inconsequential, being based on arbitrary constructs having only tenuous connection with what appears to be physical reality.

7. Quantum Calculations for Everyone

Rightfully or wrongfully, chemists have directed considerable attention to relating their experimental findings to electronic structure, even though most of the concepts of electronic structure thus employed have been qualitative and often quite speculative. Even today, much of the chemical jargon and published remarks dealing with electronic explanations of chemical effects are sufficiently vague to be rather meaningless. As computers become more efficient and more readily available, there will probably be an increasingly general use of quantum-chemical calculations. Another advance that will make such calculations cheaper and much more readily available lies in the use of trustworthy mathematical approximations in addition to those approximations presently employed in the standard calculations. We feel that the pseudopotential method is particularly advantageous in this respect. Already by this method a vast group of inorganic structures based on atoms from all over the Periodic Table have now become accessible to quantum calculations—calculations which had previously been pretty well restricted to molecules based on atoms from the first to the third period.

We believe that the chemists carrying out quantum calculations, in cases where the calculational details are of peripheral interest, would be well advised to utilize electron-density plots to aid in understanding the calculated results. Our book[5] on this subject should be a guide in this respect. In any event, only time will tell as to whether a more general use of quantum calculations across the broad spectrum of pure and applied chemistry will result in useful advances in either practical work or conceptual organization. There is a significant probability that more general use of these calculations will result in widespread disillusionment, a situation which will be of social value if this attitude extends to the present emphasis on relating physical events to mere speculations concerning electronic structure. On the other hand, an increase in the availability and reliability of quantum calculations may turn out to be really useful and to have a meaningful impact on the future development of chemistry. We hope the latter alternative will come true.

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Solid-State Photochemistry—A Method of Generating Unusual Valence States

By Gerhard Lehmann[*]

High-energy radiation can give rise to pairs of complementary defects in nonmetallic solids by the transfer of electrons between various types of atoms. These "color centers" which are generally paramagnetic, can usually be described as unusual valence states of an element. They are destroyed by heating and in most cases regenerated by renewed irradiation. In a heteropolar solid the formation of color centers usually leads to cancellation of point charges due to foreign ions of other valence or to vacancies. This is shown by the examples of kunzite, brazilianite, smoky quartz, and citrine; the most important methods for the structural elucidation of color centers are also described. Application of the principle of charge balance opens up possibilities for the production of unusual valence states, *e.g.* Al^{2+}, F^{2-}, Fe^{4+}, and O^{-}. Moreover, the type of the color center often permits far-reaching conclusions to be drawn about the defect structure of real crystals, which could hardly be clarified in other ways.

1. Basic Features of the Method

Ionizing radiation can cause three types of permanent changes in a solid.

a) The most drastic change is of course photolysis or radiolysis, and thus complete and irreversible decomposition. It is characteristic of certain compound classes, in particular of many organic compounds, which sometimes undergo characteristic changes utilized for preparative purposes[1].

b) Another possibility is a displacement of individual atoms from their equilibrium positions, *e.g.* with the formation of vacancies and interstitial atoms. Except for the alkali-metal halides, in which this takes place even with ultraviolet radiation[2], particle irradiation of higher energy is necessary in other classes of compounds.

c) Finally an electron can be transferred from a donor $D^{(-)}$ to an acceptor $A^{(+)}$. In accordance with the formal equation (1)[**]:

$$D^{(-)} + A^{(+)} \xrightarrow{h\nu} D + A \qquad (1)$$

this process usually leads to the formation of two paramagnetic defects, of which D is described as a hole center and A as an electron center. Whereas b) is a mainly physicomechanical process, which to a large extent obeys the laws of classical mechanics, c) comprises a photochemical redox process in which $D^{(-)}$ is oxidized and $A^{(+)}$ is reduced. The pioneering work of *Pohl* and his associates led to these color centers' being regarded in Germany as the domain of the physicist, and it has often been assumed that their formation is restricted to the alkali-metal halides, the classical representatives of ionic crystals. In reality, color centers can be produced in practically all crystalline or amorphous insulators. The color of many minerals is due to color centers. Among the quartzes alone we find three examples: the violet color of amethyst, the dark brown of smoky quartz, and the greenish yellow of natural citrine. The brown color of fired amethyst[3,4] is of different origin.

The basis of the photochemical redox reaction (1) is kinetic in nature: electromagnetic radiation of sufficiently high energy liberates electrons from all types of atoms. These electrons can leave the solid if they are produced sufficiently close to the surface. Photoelectron spectroscopy (XPS or ESCA = Electron Spectroscopy for Chemical Analysis)[5-8] provides a means of determining the binding energies of the electrons and their changes dependent upon valence and chemical environment. If an electron is produced in the interior of the solid, it can only migrate over a short distance before being captured by an atom—sometimes one of a different kind. As soon as $D^{(-)}$ has released its electron, it must thus compete for it with $A^{(+)}$. The situation can be visualized by considering a board with two types of depressions, some deep and narrow, some shallow and wide. If ball bearings are dropped on this board, their diameter being smaller than that of the narrow depressions, then more of them will be found in the wide than in the narrow depressions. This relationship will only be reversed if the board is shaken so vigorously that the ball bearings are repeatedly forced out of the shallow depressions. Translating these concepts into photoelectrons in a solid substance, we can therefore say that $A^{(+)}$ must have a potential well broader than that of D (*i.e.* a higher electron capture cross-section). Since, however, $A^{(+)}$ binds the captured electrons only loosely, the potential well of $A^{(+)}$ is always flatter than that of D. Therefore, reaction (1) can in most cases be reversed by heat (which corresponds to shaking of the board), and often also regenerated selectively by light:

$$D + A \xrightarrow{\text{Activation}} D^{(-)} + A^{(+)} \qquad (1a)$$

Subsequent irreversible reactions may occur particularly if neutral atoms are formed by the electron transfer (by loss of electrons from anions X^- or by electron capture by univalent cations M^+). The colloidal sodium in blue rock salt is a known example of such subsequent reactions: the primary products are electrons in anionic vacancies, the known F centers, and neutral Cl atoms (which attach themselves to the Cl^- in

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[**] The charges in parentheses on the left-hand side of equation (1) symbolize effective charges with respect to the lattice considered as neutral. Their significance will become apparent in what follows.

the lattice). Over geological periods the chlorine is lost as molecular Cl_2 and the electrons unite with the Na^+ ions to give colloidal metal particles:

$$V_{Cl} + Cl^- \xrightarrow{h\nu} e^-(Cl) + Cl^0 \qquad (2)$$
$$\downarrow Na^+ \qquad \downarrow$$
$$Na \qquad \tfrac{1}{2}Cl_2$$

(V_{Cl} = anionic vacancy; $e^-(Cl)$ = F center)

The governing principle in the formation of color centers by ionizing radiation in heteropolar solids is the balancing of point charges; this is why effective charges are given on the left in eq. (1). The formation of the F centers in NaCl is an example of this charge equalization, since a vacant anionic site is a positive point charge (and the Cl atoms are formed next to negatively charged vacant cationic sites). In oxides there are foreign atoms of different valence that are more important than the intrinsic vacancies as carriers of these point charges.

The great majority of color centers metastable at room temperature are formed according to this principle, as is found from countless examples. Thus, beryllium oxide doped with trivalent aluminum forms bivalent aluminum on irradiation[9], and on doping with fluoride the otherwise unstable fluorine dianion F^{2-} is obtained[10]:

$$Al^{3+}(\underline{Be}O) \xrightarrow{h\nu} Al^{2+} \qquad (3a)$$

$$F^-(Be\underline{O}) \xrightarrow{h\nu} F^{2-} \qquad (3b)$$

(It should be remembered that gaseous O^{2-} is also unstable and loses an electron spontaneously.) The foreign atom must be situated at a lattice site of the (underlined) host ion and not at an interstitial site if it is to be photochemically active in this way. Charge composition for incorporation of impurities with valence states different from the host ions can occur in several ways, *e.g.* in the case of incorporation of lower valence cations or higher valence anions through anion vacancies, through hydrogen in the form of OH^- groups in place of O^{2-}, or through simultaneous incorporation of a higher valence cation and a high valence anion and *vice versa*. In natural crystals a combination of these possibilities is likely to prevail, but in many instances the mechanism of charge compensation is still unknown.

It is not possible to produce bivalent lithium by doping of BeO with this metal; instead, a univalent negative oxygen is formed next to the Li^+ ion (in the language of physics, a defect electron is placed on an oxygen ion)[11,12].

$$Li^+(\underline{Be}O) \xrightarrow{h\nu} (Li^{2+}—O^{2-}) \longrightarrow Li^+—O^- \qquad (3c)$$

It can be assumed that bivalent lithium is in fact first formed, but changes to Li^+ by a very rapid electron transfer from oxygen to lithium, in which about 50 eV of energy[*] is liberated. The bracketed intermediate is thus regarded as a very highly excited state of the hole center D. Such subsequent relaxation processes can throw an obscuring cloud over much charge compensation.

Ions with empty d or f shells, such as Ti^{4+}[13], V^{5+}[14], and La^{3+}, apparently always have a large electron capture cross-section (*i.e.* they are good photochemical oxidizing agents) independently of their environment. Thus, their introduction often produces color centers whose formation contradicts the charge equalization principle, as the following examples show:

$$Ti^{4+}(\underline{Si}O_2) \xrightarrow{h\nu} Ti^{3+} \qquad (4a)$$

$$V^{5+}(NaAl_3(\underline{P}O_4)_2(OH)_4) \xrightarrow{h\nu} V^{4+} \qquad (4b)$$

Knowledge and planned application of these principles makes it possible to generate unusual valence states that are often unobtainable in any other way. These reactions have so far been hardly utilized; apart from preparative applications, conclusions about disorder in real crystals can be drawn from the structure of the color centers.

2. Limitations of the Method

Although the examples given above are most impressive, there are limitations to the method apart from the relaxation to an energetically more favorable state as shown in reaction (3c). To be certain of a sufficiently long life of the color center, the potential well of A must be deep enough in comparison with the thermal energy kT and similarly the bottom of the potential well of D must be sufficiently separated from the valence band. If these conditions are not fulfilled, the color centers will be destroyed by recombination of the electrons with defect electrons. This recombination can occur by excitation of an electron from the electron center A into the conduction band or excitation of an electron from the valence band into the hole center D and subsequent migration of the electron (or the hole in the valence band) to the complementary center. The energy relationships are illustrated schematically in Figure 1. The principle of charge compensation is barely perceptible in the structure of color centers stable

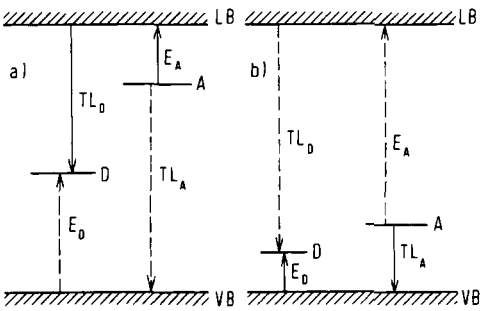


Fig. 1. Schematic representation of the position of defect electron centers D and electron centers A between the valence band VB and the conduction band LB. a) On thermal destruction of the color centers (recombination), electrons are excited from A into the conduction band, since the activation energy $E_A < E_D$. Thermoluminescence TL_D is then possible. b) On recombination electrons are excited out of the valence band, since $E_D < E_A$. The thermoluminescence corresponds to TL_A. Case b) occurs with the color centers in smoky quartz and citrine (see Section 5).

[*] 1 eV ≙ 23 kcal/mol or about 100 kJ/mol.

only at very low temperatures, because here very shallow potential wells are already effective.

Since foreign ions of different valence cannot be included in any desired concentration, the color centers are always produced in a dilute state. The attainable concentrations of such foreign ions are usually around 0.1 mol-% or below, and often much lower still on crystallization from solutions. Only rarely, as in the case of ammonium halides, can concentrations in the percent region be attained. In the modifications of ammonium halides of CsCl structure, ions such as Mn^{2+} and Cu^{2+} occupy an interstitial position between two NH_4^+ sites, so that they are surrounded by four halide ions in square-planar configuration. Neutral water molecules can be included in place of the missing ammonium ions, so that the transition-metal ions have a compressed octahedral coordination, as investigations of the electron spin resonance[15-17] and optical absorption[18-20] have shown.

Electron and defect electron centers must be separated from one another by at least about 50 Å, for otherwise spontaneous recombination, in some circumstances very slow, may occur by the quantum-mechanical tunneling process. In contrast to the migration of electrons by way of the conduction or valence bands, the tunneling process is not thermally activated and thus cannot be prevented by cooling.

An example of tunnel recombination is provided by the semiprecious stone kunzite, a lithium aluminum silicate of composition $LiAlSi_2O_6$ (spodumene) containing at the most 1 % of manganese (see Section 3). Part of the initially bivalent built-in manganese obviously passes on irradiation through a trivalent state (rose-violet), which occurs in most of the natural crystals, into the tetravalent state (green)[21] that is rarely observed in nature. Part of the tetravalent manganese (5 % was measured in one crystal)[22] decomposes over a period of a few days to the trivalent state with the emission of an intense yellowish luminescence characteristic of Mn^{2+} in sixfold coordination. The intensity of this emission decreases only slowly with time (in inverse proportion to the square root of the time), and is barely changed when the crystal is cooled to liquid-nitrogen temperature[21]. As shown in Figure 2, there is no systematic temperature variation of the decomposition rate between 16 and 86 °C.

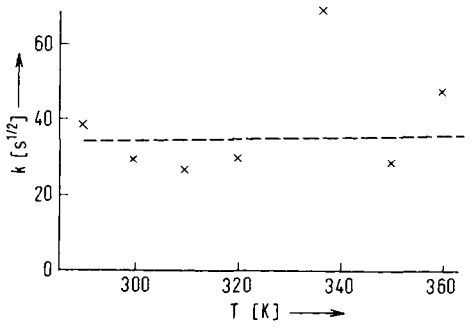


Fig. 2. Rate constants k for spontaneous decomposition of the green color centers (Mn^{4+}) in kunzite. The decomposition follows the rate equation

$$I = I_0 \cdot k/(k^2 + t)^{1/2}$$

where I = luminescence intensity is a measure of the rate. Within the limits of experimental error it was not possible to establish any temperature dependence of the rate constants.

Even if, as in this example, foreign ions can be included in higher concentrations, because of the necessary spatial separation between the electron and defect-electron centers their concentrations are limited to relatively small values, typically about 100 ppm. With foreign ions of different valence the preservation of neutrality requires further defects, and these are normally also point charges in the lattice. Thus, centers complementary to each other can be formed, as for example in the case of the alkali-metal halides: anionic vacancies take up electrons and form F centers as electron centers, and defect-electron centers (Cl^0) are formed directly next to the cationic vacancies. A condition for this is again the minimal spatial separation. Either the charge equalization must take place at some position further removed and not next to the foreign ion, or the defect must be able to migrate out of the neighborhood of the foreign ion immediately after the electron transfer, the absence of electrostatic attraction thus being a favorable prerequisite for charge compensation. Thus, alkali-metal ions present in quartz next to aluminum can diffuse away at room temperature in the formation of smoky quartz centers on the aluminum[23]. Hydrogen in the form of OH groups cannot do this in the neighborhood of aluminum, and this is probably why Al—H defects cannot be changed into smoky quartz centers[24]. The minimal spatial separation is one reason why introduction of foreign ions of different valence does not always lead to the formation of color centers at or next to these foreign ions.

In Sections 3 to 5 it will be shown in greater detail on selected examples how solid-state photochemistry can be used to produce unusual valence states and how conclusions about the defect structures of real crystals can be drawn from the structure of color centers formed. Since little is generally known about these possibilities, so that they have not been widely utilized, the examples must be drawn from nature, and they are chosen so that emphasis of each brings out the advantages and the limitations of a particular method of investigation.

3. Color Centers in Kunzite

The rose-violet or green color centers in kunzite (spodumene $LiAlSi_2O_6$) are obtained only in the presence of manganese (present in the bivalent state), so that manganese must be involved in the formation of the color centers. The depth of color and the contents of trace elements were correlated with one another some time ago for the allochromatic minerals, *i.e.* minerals variously colored by foreign atoms, but often and particularly where the measurements had been most exact, the proportionality between the content of foreign atoms and the depth of color is not very good. Today we can easily account for the failure of this correlation. On the one hand complementary defects $D^{(-)}$ and $A^{(+)}$ are needed for the formation of color centers, and it is possible that only one kind of defect-electron centers but several kinds of electron centers (or *vice versa*) may be present in conditions that change from crystal to crystal. On the other hand the foreign atoms are often present in various arrangements, only one of which is capable of forming color centers.

In kunzite a stepwise transfer of a total of two electrons takes place[21], whence it seems reasonable to assume the

formation of higher valence states of the manganese. This assumption can be tested by means of the optical spectra of the rose-violet and the green color centers. Since the ligand field theory predicts within narrow limits the number and the position of the bands for these valence states as a function of the geometry of the surrounding anions, and since we can also estimate the intensities from the wealth of experience, we can therefore decide which positions in the lattice can be occupied by the color-center-forming manganese. The manganese can occupy the lattice sites of the lithium, the aluminum, or the silicon. In spodumene lithium and aluminum are sixfold coordinated in distorted octahedral symmetry, whereas the silicons are surrounded by oxygens in distorted tetrahedra. Absorption spectra of the green color centers are shown in Figure 3. These spectra were recorded in linear polarized light. The pronounced anisotropy of the intensity proves that we are dealing with oriented and thus atomically distributed absorption centers of low symmetry.

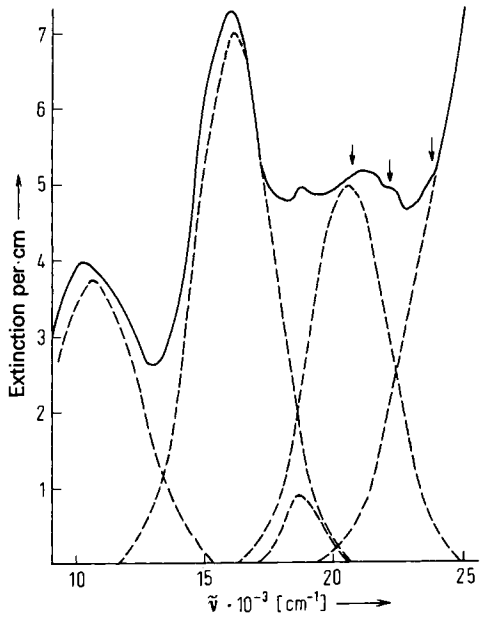


Fig. 3. Optical absorption of the green color centers (Mn^{4+}) in kunzite, measured at 78 K with linearly polarized light, whose electrical vector is oriented parallel to the crystal *a*-axis. Other orientations give the same bands in other intensity ratios. The arrows indicate Mn^{2+} absorptions.

The spectrum in Figure 3 cannot be explained on the basis of tetravalent manganese in approximately octahedral coordination because, since Mn^{4+} is isoelectronic with Cr^{3+}, the Mn^{4+} spectrum should be analogous to the Cr^{3+} spectrum, except that due to the greater ligand field strength parameter of manganese(IV) the bands should be at higher wave numbers compared with chromium(III). Thus, with octahedral coordination the first moderately intense (spin-allowed) band should occur at about 23000 cm^{-1}[25]. The spectrum can, however, be explained very well by a distorted tetrahedral coordination of Mn^{IV}[21]. This would then indicate that at least part of the bivalent manganese is present at the lattice sites of the silicon. Because of the differences in ionic radii and valence states this at first appears surprising, but it has been demonstrated in garnets by Mössbauer investigations that bivalent iron to some extent occupies the tetrahedral sites of the silicon[26]. The trivalent manganese (rose-violet) must then also be present in distorted tetrahedral coordination. The spectrum shown in Figure 4 can be explained on the basis of an approxi-

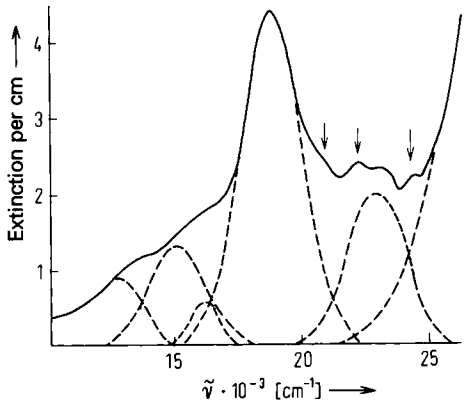


Fig. 4. Optical absorption of the rose-violet color centers (Mn^{3+}) in kunzite. Measurement conditions as in Fig. 3. The arrows indicate Mn^{2+} absorptions.

mately octahedral or a distorted tetrahedral arrangement of Mn^{III}, and was evaluated by *Recker et al.*[27] as an indication of Mn^{III} at the lattice sites of the aluminum. This ambiguity has its origin in the properties of the d^4 configuration, which (like the d^9 configuration of bivalent copper) leads to an orbit-degenerate ground state in octahedral or tetrahedral coordination. Deviations from the cubic symmetry remove this degeneracy, at least partially; the associated energy gain should cause spontaneous distortion. This Jahn-Teller effect[28, 29] has been demonstrated in a considerable number of compounds[30]. It also stops compounds such as $Cu^{II}M_2{}^{III}O_4$ and $M^{II}Mn_2{}^{III}O_4$ from crystallizing in the cubic spinel structure, at least at low temperatures.

Figure 5 shows that splitting of the ground state leads to an average transition energy, which is higher than can be expected from the magnitude of the ligand field strength parameter *Dq*. The ratio of the excitation energies of distorted tetrahedral and of octahedral complexes of these ions is thus distinctly greater than the ratio (about 0.6) of *Dq* values that can be obtained from electrostatic calculations with consideration of the approximately 6% shorter bond length in the tetrahedral case.

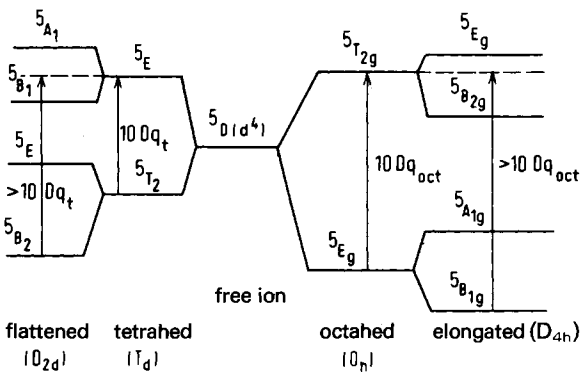


Fig. 5. Energy levels of Mn^{3+} in octahedral and tetrahedral symmetry and with additional (tetragonal) distortion.

The position of the more intense electron-transfer bands at higher energies can also be estimated within narrow limits by means of the concept of optical electronegativities[31]. The position of the absorption edges for the rose-violet and green color centers agrees well with the values calculated for Mn^{III} and Mn^{IV}[21].

On grounds of intensity the ligand field spectra of lower-valence transition metal ions are generally unobtainable as color centers. The optical spectra can never be regarded as proof of a specific structure of the color centers, although some structures can be excluded and others made probable.

Electron paramagnetic resonance is extremely important for the structural elucidation of color centers. The deviation of the g factors from the value for the free electron can be used to yield information on the position of the excited state by means of eq. (5) (where n is a small integer):

$$\Delta g = n \cdot \lambda / \Delta E \qquad (5)$$

This information can then be compared with the optical spectrum. The spin-orbit coupling parameter λ is known within narrow limits. Since according to Hund's third rule it changes its sign with a half-filled shell, the direction of the deviation shows whether an electron center with $g < g_{free}$ or a defect-electron center with $g > g_{free}$ is present. Further information can be provided by hyperfine or superhyperfine[*] splitting of the signal; this splitting arises by interaction of the electron spin with the nuclear angular momentum I on the paramagnetic atom or in its environment. The number m of lines gives the magnitude of the nuclear angular momentum from $m = 2I + 1$; if there are several equivalent nuclei, one obtains the number of lines corresponding to the total angular momentum, in intensity ratios given by binomial coefficients, as is known for organic radicals[32]. Finally, the magnitude of the splitting is determined by the electron distribution; for example, the isotropic fraction is proportional to the s-electron density on the nucleus with angular momentum I. In a single crystal these quantities are in general anisotropic, so that information is also obtained about the orientation of the centers in the lattice. A very good review of color centers in inorganic substances, with findings up to about 1966, has been given by *Atkins* and *Symons*[33], who also treat the principles of EPR spectroscopy more rigorously.

Neither trivalent nor tetravalent manganese could yet be detected in spodumene by EPR, but it was possible to show the participation of Mn^{II} in the formation of the green color centers. Thus, on the conversion of the green into the rose-violet color centers the intensities of the EPR spectra of Mn^{II} increase by a few percent, while for Fe^{III} even an increase of about 20 % was observed[22]. This is explained most simply by assuming that both bivalent manganese and trivalent iron can act as acceptors $A^{(-)}$, *i.e.* are partially converted into univalent manganese or bivalent iron (though the EPR spectra of these species could only be observed at low temperatures).

In the case of iron in amethyst it was concluded some years ago from the optical spectra and the changes in the EPR spectra of trivalent iron that the cause of the coloration was tetravalent iron at the sites of the silicon (and bivalent iron in interstitial positions)[3]. Recently an EPR signal was observed from a center with total spin $S = 2$[34], which could arise from either bivalent or tetravalent iron; the small line width at room temperature makes it extremely improbable that bivalent iron is the cause.

A direct proof of the presence of tetravalent manganese in kunzite would be very interesting, because here there appears to be a tetrahedral low-spin complex with $S = 1/2$[21] and because Mn^{IV} has not yet been proved with certainty to exist in tetrahedral coordination[35]. Because of the large parameter Dq, the ligand field stabilization energy (greater even than for Cr^{III}) favors octahedral over tetrahedral coordination by about 50 kcal/mol. If Mn^{II} is present and is photochemically converted into Mn^{IV}, there is no point in asking which coordination is favored by Mn^{IV} during the growth of the crystal; it remains to be discovered whether nature selects the route *via* Mn^{II} outlined above.

4. Color Centers in Brazilianite

Brazilianite is a sodium aluminum hydroxyphosphate of composition $NaAl_3(OH)_4(PO_4)_2$, which crystallizes in the monoclinic space group $P2_1/c$[36]. It occurs in nature in well-formed green to brown crystals, the color being due at least indirectly to color centers. Brazilianite is composed of elements which, except for oxygen, consist of only one isotope with nonzero nuclear angular momentum I: ^1H and ^{31}P with $I = 1/2$, ^{23}Na with $I = 3/2$, and ^{27}Al with $I = 5/2$. Thus, in every case the EPR signals should exhibit superhyperfine splitting, which facilitates elucidation of the structure.

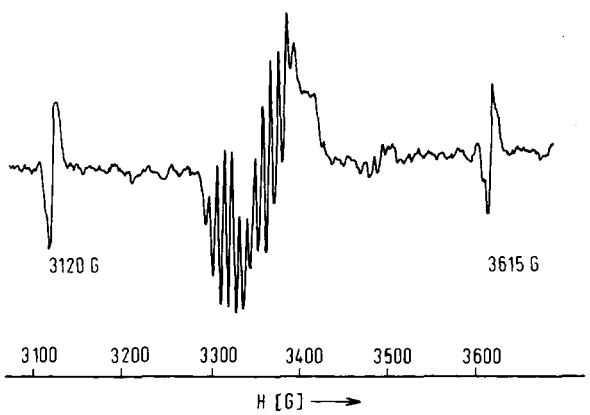


Fig. 6. Section of the EPR spectrum of irradiated brazilianite. The multiplet in the middle is derived from hole centers $Al^{3+}—O^-—P^{5+}$ and the two outer signals are due to atomic hydrogen. Microwave frequency 9.6 GHz, c- and b-axes of the crystal perpendicular to the magnetic field.

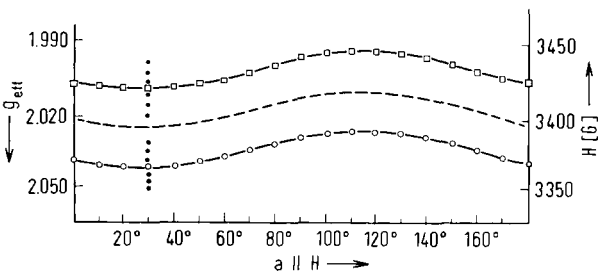


Fig. 7. EPR spectra of the defect electron centers in brazilianite on rotation around the b-axis. All the shf lines are indicated (●) only for one orientation, for other orientations only the center-point of the sextets (□ and ○). The broken line shows the center-points of doublet splitting.

[*] Known as the hf or shf structure.

A section of an overall spectrum is given in Fig. 6; a signal with a total of twelve lines can be seen in the middle. Figure 7 shows how the position of this signal changes with rotation around the twofold axis of the crystal. It consists of two sextets separated by about 50 gauss, the midpoint being at g factors above the value for a free electron (2.0023). Since the sextet splitting can arise only from the aluminum (no other nuclei with $I = {}^5/_2$ are present, according to trace analysis, in sufficient amounts), we must have here an O^-—Al^{3+} center in which the unpaired electron has a small electron density at the aluminum nucleus. The additional doublet splitting can originate from a phosphorus atom or a proton. A proton can almost certainly be ruled out, for two reasons: In the first place, because the electronegativity of OH is greater than that of O^-, a defect electron on an OH group would not be stable; secondly, the splitting may amount only to about 20 gauss. Then an Al^{3+}—O^-—P^{5+} center must be present. Remaining doubt could be removed by replacement of the hydrogen by deuterium, which with its $I = 1$ should give triplet splitting.

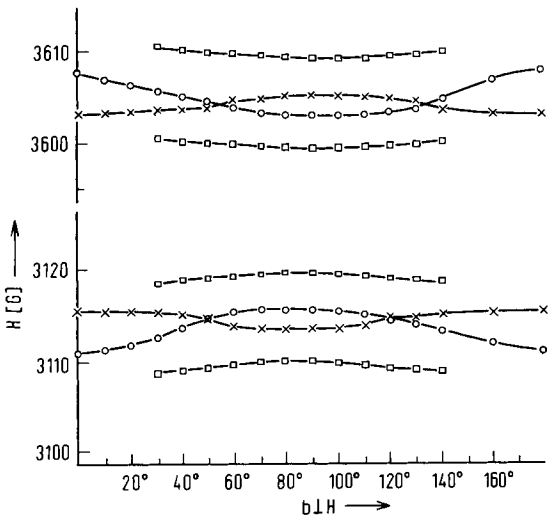


Fig. 8. EPR spectra of the hydrogen atoms in brazilianite on rotation around the c-axis. The atomic hydrogen is present in three arrangements; the additional doublet splitting in one arrangement (□) indicates the proton of an OH group.

In Figure 6 two other signals can be recognized, with a separation of about 500 gauss. Figure 8 shows that these must originate from atomic hydrogen (for which the hfs splitting of about 500 gauss is characteristic) at three lattice positions.

The structure of these color centers is thus in principle clarified, as is that of the previously mentioned V^{4+}, which gives an octet as a result of splitting due to ^{51}V with $I = {}^7/_2$. It is more difficult to say from which defects the color centers are formed. Atomic hydrogen is not found in native crystals; it is formed by artificial irradiation and is destroyed already at 160 °C, whereas the defect electron center Al^{3+}—O^-—P^{5+} is stable up to 190 °C. Atomic hydrogen cannot be formed from the stoichiometric OH groups of the mineral; this is shown by experiments in which the hydrogen was repeatedly removed by heating and regenerated by irradiation. It was then found that one of the hydrogen spectra appeared increasingly weakly, which can only be explained by an impoverishment of the crystal in this hydrogen. Here then is a case where electron centers and defect electron centers are destroyed separately and, at least in part, irreversibly.

The twelve oxygen atoms of the empirical formula have three different coordinations: 2 Al and 1 H (4 O), 2 Al and 1 P (2 O), and one each of Al, P, and Na (6)[36]. Only the last two coordinations come into question as carriers of defect electrons. Thus, in the second, one Al could be replaced by Mg or Zn (other bivalent ions are excluded by trace analyses, except for Fe^{2+} which, however, passes into Fe^{3+}). An additional shf splitting by ^{25}Mg or ^{67}Zn with $I = {}^5/_2$ and 10 % abundance (4.1 % for ^{67}Zn) would then be observed, which is not the case. Furthermore, the defect electron spectrum can also be produced in (polycrystalline) synthetic brazilianite not doped with magnesium or zinc. This possibility therefore appears unlikely and we must consider a partial replacement of sodium by hydrogen in the form of OH groups and formation of the color centers by:

$$Al^{3+}—\overset{\overset{H}{|}}{O}^-—P^{5+} \xrightarrow{h\nu} H + Al^{3+}—O^-—P^{5+} \qquad (6)$$

The formation of atomic hydrogen in a number of other phosphates[33] makes this kind of disorder plausible—it corresponds to partial formation of an acid phosphate. Its extent should increase with decreasing pH of the solution from which the crystals are grown. Tests should be carried out on model substances to see whether the amount of atomic hydrogen produced depends on pH.

5. Color Centers in Smoky Quartz and in Citrine[37]

In spite of the different colors of smoky quartz (brown-black) and citrine (yellow) their color centers are closely related; the cause of the difference is unknown. Comparative experiments on their decomposition kinetics have, however, contributed considerably to solution of this problem.

In smoky quartz defect electrons are present on oxygen next to a substitutional aluminum[23]; the principle of charge equalization is thus also recognizable here. The defect electrons can be exchanged at relatively low temperature between the oxygen ions of the AlO_4 tetrahedra[*][38]. It is thus understandable why the line width of the EPR signals increases above 20 K; they are therefore not observable at room temperature. Only one of the absorption bands in the visible region ("A_3 band" at 23800 cm^{-1}) originates from the smoky quartz centers[39]; the origin of the longer-wave A_1 and A_2 bands at 14900 and 20600 cm^{-1}, respectively, is still unknown. According to *Schirmer*[40], the light-induced transfer of the defect electron between two equivalent oxygen ions is the cause of the A_3 band. This model is in agreement with all previous experience. If, as in the case of the hole center in brazilianite, the defect electron is localized on one particular oxygen (as indicated by the sharpness of the EPR spectra at room temperature), then there will be no absorption bands in the visible region, because excitation within the 2p level of oxygen is Laporte forbidden; thus, only weak absorption can be obtained there, and other excitations

[*] In fact the point symmetry of the silicon in α-quartz is only C_2, so that there are two pairs of oxygens with slightly different bond lengths.

occur with much higher energies. If, however, the defect electron can be exchanged between oxygen ions of the same valence, as in the O^-—Li^+ center in BeO[11,12] and probably also in the felspar sanidine[41], then we find broad and intense absorption bands in the visible region of the spectrum.

In the color centers of natural citrines defect electrons are also adjacent to an aluminum[42]. This is shown, *inter alia*, by the EPR spectra in Figure 9. One can recognize a sextet very well resolved at room temperature, together with less well resolved lines at somewhat lower magnetic fields. At

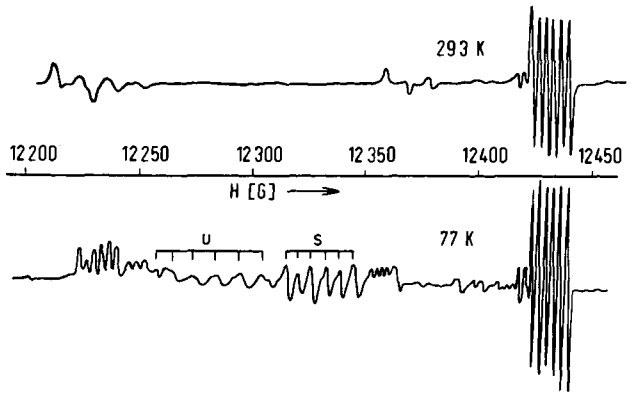


Fig. 9. EPR spectra of natural citrine at 34.8 GHz, magnetic field approximately parallel to the threefold axis of the crystal. At 77 K there appear additional sextets from smoky quartz centers (S) and from centers of unknown structure (U). In the selected orientation only one sextet from smoky quartz centers is present, but several from the citrine centers, which must thus be present in various orientations.

77 K the latter's resolution is somewhat better and there is a sextet of smoky quartz centers (S) present in a lower concentration together with the signal of another center of unknown structure (U). The citrine centers produce an uncharacteristic slightly anisotropic increase in optical absorption up to the UV, but no band in the visible region. In contrast to the situation at the smoky quartz center, the defect electron at the citrine center is thus localized on one oxygen atom. One of the four possible oxygens must be so energetically favored as a carrier of the defect electron that the latter's exchange is no longer recognizable at room temperature. Greater bond lengths lead to a gain in energy. For the difference in Si—O separations of the oxygen pairs in α-quartz, of the order of 0.01 Å[43], an energy difference of 0.7 kcal/mol has been measured for smoky quartz centers, in good agreement with the value calculated on the basis of electrostatic concepts[38].

Only in favorable cases can decomposition kinetics yield information about the stability of a color center. If electron and defect electron centers are destroyed at the same time, we must know whether recombination occurs *via* excitation of the electron into the conduction band or by excitation of the defect electron into the valence band (see Figure 1). Destruction of the smoky quartz or citrine centers is accompanied by thermoluminescence, *i. e.* an emission of light. Their spectral distributions are shown in Figure 10.

In both cases, therefore, the energy stored on irradiation is, with a high probability[*] emitted as light. The emission

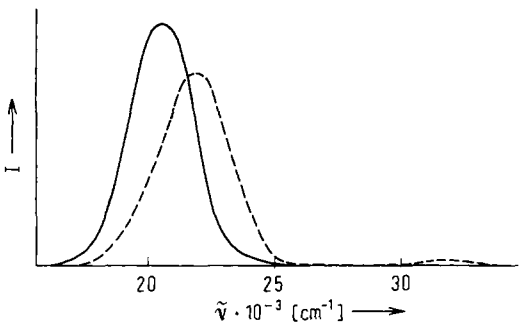


Fig. 10. Thermoluminescence of smoky quartz centers (——) and of citrine centers (----). The intensities I are not normalized to the same center concentrations.

maxima give the distance of the electron center from the valence band in cases of defect electron excitation. If the electron is excited, the distance of the defect electron center from the conduction band is involved. The main band in citrine is displaced to higher energies than that in smoky quartz. Since, however, a greater stability of defect electron centers means a larger distance from the valence band and therefore a smaller one from the conduction band, the emission can only represent the separation of the electron centers from the valence band; it must therefore be the defect electron that is excited. If this excitation is the rate-determining step in the destruction of the color centers, the activation energy for the reaction can be determined from the separation of the defect electron centers from the valence band. The difference between activation energies gives the energy difference between the smoky quartz and the citrine centers. As isothermal measurements of the destruction of optical absorption of the two centers have shown, the reaction orders are close to unity; consequently, excitation of the defect electron is indeed rate-determining. The activation energies are about 36 kcal/mol for citrine and about 30 kcal/mol for smoky quartz. These values were checked by measuring the temperature maxima of the emission intensities during rapid linear heating of the samples. Figure 11 shows the glow curves obtained, from whose maxima the activation energies can be calculated[44]. They are in good agreement with the values measured isothermally (the smoky quartz centers gave, because of the two maxima, two values close together). This good agreement is proof that the same process lies at the basis of thermoluminescence and the destruction of absorption bands.

The additional stabilization of the citrine centers amounts to about 6 kcal/mol. The cause of this stabilization is still unclear; it seems reasonable to assume an extension of one

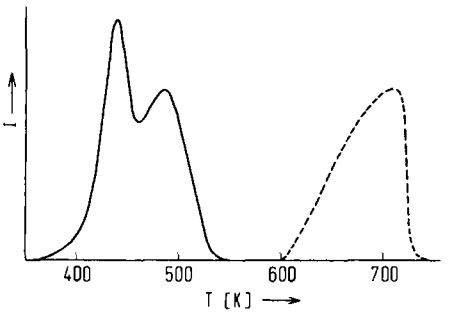


Fig. 11. Glow curves for smoky quartz centers (——) and citrine centers (intense emission bands) (----). Heating rates 3.5 and 6 K/min.

[*] This can be expressed quantitatively as the quantum yield (number of light quanta emitted per center decomposed).

aluminum-oxygen distance to a value close to the normal Al—O bond length (1.74 Å[45]). (The normal Si—O bond is only 1.61 Å[43].) Only the absence of a neighboring silicon or oxygen atom could cause an increase of this magnitude. Since these vacancies are not thermodynamically stable, they perhaps could be formed by high-energy particle irradiation. At the moment it is only certain that smoky quartz centers consist of a defect electron on an undisturbed AlO_4 tetrahedron, while there is an additional fairly large disturbance at the citrine centers[*].

6. Prospects

All the examples in this review have been taken from the realm of naturally occurring minerals. It seems pertinent to imitate nature and to draw conclusions from the results, *e.g.* about the growth conditions of natural crystals. In some cases this has already been done as for smoky quartz and amethyst, but in others (citrine) the attempts so far have been unsuccessful. Knowledge of the principles of formation enables plans to be drawn up for a systematic synthesis of unusual valence states or for unfavorable coordination of specific ions, and then to select the most favorable plan for the experimental synthesis. Since the incorporation of charged point defects is nearly always a prerequisite for success, it is in general more promising to grow the crystals from the melt rather than from solution, because then the crystal can much more easily be forced to pick up foreign atoms. Undesirable thermal reductions, such as that of Cu^{II} to Cu^{I} in the growth of doped cadmium halide crystals from melts, can be reversed by subsequent irradiation. In the case of $CdBr_2$ defects are formed during crystal growth, with a still unknown structure[47]:

$$Cu^{2+}(CdBr_2) + Br^- \xrightarrow{kT} Cu^+ + Br \longrightarrow A^{(+)} \qquad (7)$$

The energy of ultraviolet radiation suffices for re-formation of bivalent copper[46]:

$$Cu^+(CdBr_2) + A^{(+)} \xrightarrow{h\nu\,(UV)} Cu^{2+} + A \qquad (8)$$

It must also be possible in this way to prepare Cu^{2+} in CdI_2, *i.e.* a diluted CuI_2, and to investigate it.

There are many possible applications to structural problems. Here let us consider only the question of the blue coloration of corundum by bivalent iron. In crystal growth by the Verneuil process or from melts bivalent iron is obtained in place of trivalent on simultaneous doping with titanium. The blue color of such crystals has been explained[48,49] by an intervalence transition between Fe^{II} and Ti^{IV}, which is possible only if Fe^{2+}—O^{2-}—Ti^{4+} complexes are present, *i.e.* if charge compensation occurs in the immediate neighborhood of the Fe^{II}. Against this interpretation is, among other things, the fact that natural blue sapphires contain hardly any titanium[50]. Here, because of the different conditions of growth, the charge is equalized in a different way, probably through OH groups. The blue color of natural sapphire is readily explained by ligand field transitions of Fe^{II}[51]. The blue color of the synthetic crystals is destroyed by X-ray irradiation, apparently because of the reaction:

$$Fe^{2+}(\underline{Al_2O_3}) + Ti^{4+}(\underline{Al_2O_3}) \xrightarrow{h\nu} Fe^{3+} + Ti^{3+} \qquad (9)$$

which, however, is possible only if the two ions are not next to each other. Although direct proof of eq. (9) has not yet been provided, the sapphire question indicates well the variety of problems to whose solution solid-state photochemistry can contribute.

I am indebted to Dr. A. Räuber, Institut für Angewandte Festkörperphysik der Fraunhofer-Gesellschaft, Freiburg, for the Q-band EPR spectrum of citrine. The examples were largely taken from our own work which was supported partly by the Deutsche Forschungsgemeinschaft and partly by the Ministerium für Wissenschaft and Forschung des Landes Nordrhein-Westfalen.

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[*] According to recent results, the citrine center appears to be an O_2^-—Al defect.

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Interpenetrating Polymer Networks

By Daniel Klempner[*]

Besides mechanical blending and copolymerization there is a third possible way in which two polymers can be combined. Each polymer forms its own network, while both networks interpenetrate each other. There are no covalent bonds between the polymers. Such interpenetrating networks have been synthesized sequentially (from polymer A and monomer B) and simultaneously (from monomer A and monomer B). It is preferable that the polymers be of different chemical type; usually, an elastomer and a glass are combined, *e.g.* a polyurethane and a polyacrylate. Depending upon the ratio of component polymers either a strengthened elastomer or a glass having impact strength is formed. So far, there are no direct methods for establishing the degree of interpenetration.

1. Introduction

The chemical and physical combination of two or more structurally dissimilar polymers has been of commercial and academic interest for a number of years, since it provides a convenient route for the modification of properties to meet specific needs. It has been used to facilitate processing and to impart flexibility, tensile and impact strength, chemical resistance, weatherability, flammability resistance, and a variety of other properties[1-4]. The physical properties of the combined polymers depend not only on the properties of the constituent polymers but also on the way they are combined.

Mechanical blending is the oldest way of physically combining two or more linear polymers and is accomplished by mixing the polymers in a liquid state, *e.g.* melt, solution or dispersion.

Chemical combinations of polymers can be defined as the combination of two or more types of polymers (or corresponding monomers) generally *via* covalent bonds and can be achieved by random, alternate, block, or graft copolymerization.

Interpenetrating polymer networks (IPN's) are a novel type of polymer blend composed of crosslinked polymers. They are more or less intimate mixtures of two or more distinct crosslinked polymer networks with no covalent bonds between the polymers, *i.e.* polymer A crosslinks only with other molecules of polymer A, as does polymer B. A schematic representation of an ideal IPN is shown in Figure 1.

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Thus, IPN's may be described as combinations of chemically dissimilar polymers in which the chains of one are completely entangled with those of the other. The entanglements must

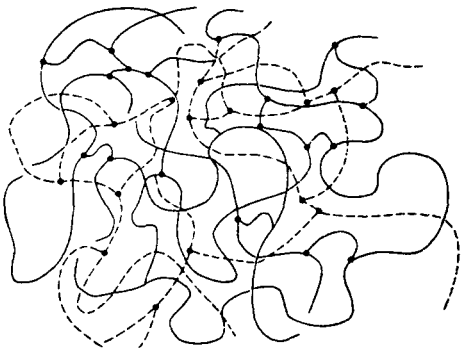


Fig. 1. Ideal Interpenetrating Polymer Network (IPN). —— Polymer A, ... Polymer B.

be of a permanent nature and are made so by this homocrosslinking of the two polymers. IPN's can be of various chemical types and can be synthesized in a variety of ways. There are two basic techniques for producing IPN's. In the first, a crosslinked polymer of type A is swollen with a second monomer of type B, plus crosslinking agents. This is followed by the polymerization and crosslinking of polymer B *in situ*. The second consists of combining the linear polymers, prepolymers, or monomers of the two polymer types, together with their respective crosslinking agents, in some liquid form, *e.g.* bulk (melt), solution, or dispersion. This is followed by the simultaneous polymerization and crosslinking of the two polymers. Care must of course be taken in the selection of

the polymers to prevent reaction occurring between them. It is also preferable that the polymers be of different chemical types so that the resulting material will be more than just a copolymer. Interest centers in these materials for a variety of reasons. Some of the more important ones are discussed below:

1. IPN's represent a mode of blending two or more polymers to produce a mixture in which phase separation is not as extensive as would be otherwise. In fact, it is the only way of combining crosslinked polymers. Normal blending or mixing of polymers results in a multi-phase morphology due to the well known thermodynamic incompatibility of polymers. This incompatibility is due to the relatively small gain in entropy upon mixing the polymers due to contiguity restrictions imposed by their large chain length[5]. However, if mixing is accomplished on a lower molecular weight level, and then polymerization accomplished simultaneously with crosslinking, phase separation may be kinetically controlled since the entanglements will have been made permanent by the crosslinking. In other words, phase separation cannot occur without breaking covalent bonds.

IPN's synthesized to date exhibit varying degrees of phase separation, dependent principally on the compatibility of the polymers. With highly incompatible polymers, the thermodynamics of phase separation are so powerful that it occurs substantially before the kinetic ramifications (*i.e.* crosslinking) can prevent it. In these cases, only small gains in phase mixing occur. In cases where the polymers are more compatible, phase separation can be almost completely circumvented. Note that complete compatibility (an almost impossible situation) is not necessary to achieve complete phase mixing, *i.e.* interpenetration, since the "permanent" entanglements produced by interpenetration prevent phase separation. With intermediate situations of compatibility, intermediate and complex phase behavior (morphology) results. Thus, IPN's with dispersed phase domains ranging from a few microns (the largest)[6], to a few hundred ångströms (intermediate)[7], finally to those with no resolvable domain structure (complete mixing)[8] have been reported.

2. IPN's represent a special example of topological isomerism[9] in macromolecules[10]. Some permanent entanglements between the different crosslinked networks are inevitable in any sufficiently intimate mixture of the crosslinked networks. These represent examples of catenation in polymer systems, *i.e.* different ways of imbedding these molecules in three dimensional space. Permanent entanglements are hindering constraints on the motion of segments and ought to simulate covalently bound chemical crosslinks[11]. Simplified theoretical models of such permanent entanglements[12] exhibit a surprisingly large non-linear elastic restoring force unlike that expected with chemical crosslinks from ideal rubber elasticity theory.

3. The combining of varied chemical types of polymeric networks in different compositions, often resulting in controlled different morphologies, has produced IPN's with synergistic behavior. For example, if one polymer is a glass (glass transition, T_g, above room temperature) and the other is elastomeric (T_g below room temperature), one obtains a reinforced rubber, if the elastomer phase is the continuous, predominant one, or a high impact plastic if the glassy phase is continuous[13]. In the case of more complete phase mixing, enhancement in numerous mechanical properties is due to the increased physical crosslink density due to this interpenetration. IPN's have been synthesized with intermediate maxima *versus* network composition in bulk properties such as tensile strength[14–22], impact strength[16,17], and thermal resistance[16–18,20], and minima in surface properties such as critical surface tension. Certain of these synergistic properties of IPN's such as the mechanical properties reflect their special architecture. Others such as thermal resistance, may simply be consequences of the fact that IPN's are usually blends of different chemical types of networks and may have little to do with their special structure[23].

In this paper, we shall present a brief historical review of IPN's since their inception, including their synthesis, morphology, and classification. We shall then discuss some of the most important developments in recent years and present some of the prominent unsolved problems.

2. Synthesis, Classification, and Morphology

In an excellent review of IPN's, *Sperling*[24] points out that ... "the IPN topology was long known and apparently 'rediscovered' several times." He cites patents dating from the forties in Great Britain and the fifties in the United States. Thus, *e.g. Staudinger* and *Hutchinson*[25] describe the use of IPN's to produce smooth sheets of bulk polymerized homopolymers while *Solt*[26] somewhat later described the use of anionic and cationic IPN's as ion exchange resins. The term IPN was first introduced by *Millar*[27], who studied "homo-IPN's" in which both polymer networks were composed of polystyrene crosslinked with divinylbenzene. He prepared a series of these IPN's by allowing the first crosslinked polystyrene network to imbibe a calculated amount of a suitable mixture of styrene and a 50% divinylbenzene-toluene solution, containing catalyst, and then polymerizing the imbibed monomers within the original polymer network. *Millar* found a small increase in density of the resultant network which he ascribed to interpenetration.

Shibayama and *Suzuki*[28,29] studied the viscoelastic properties of such polystyrene homo-IPN's prepared in a manner similar to those prepared by *Millar*. But they found practically no difference in density between a control polystyrene network and the IPN. They did find, however, much larger crosslink densities in the IPN's. Besides additional crosslink formation by chain transfer and extension of the original network, these authors ascribed the increase in crosslink density to the increase in entanglements caused by the superposition of the networks. They found as expected an increase in rubber modulus, a decrease in swelling tendency (in agreement with *Millar*), while the glass transition temperature and the viscoelastic properties in the glass-to-rubber transition region were not much altered. Other such homo-IPN's were synthesized by *Shibayama et al.*[29,30] and more recently by *Clark*[31].

A number of different IPN nomenclature schemes have been introduced. A very simple scheme[32] is based on morphology, topology and method of synthesis. According to this scheme essentially all of the above examples of IPN's are sequential interpenetrating polymer networks (SIPN). SIPN's are formed by the swelling method outlined above; they are

termed sequential since one material is completely polymerized and crosslinked while the other is still a monomer. In this scheme *Millar*'s homo-IPN's are called interpenetrating homopolymer networks (IHPN). A much more extensive classification scheme has been recently developed[33] which considers the nature of the reactive unit (*e.g.* monomer, crosslinker, *etc.*) the operation involved (*e.g.* polymerization of monomer, grafting, *etc.*) and most importantly the sequence of operations.

Since 1969, two groups independently developed systematically the concept of IPN's composed of two or more chemically different polymers. Initially *Frisch et al.*[14,34] produced a latex interpenetrating polymer network (LIPN) by mixing dispersions, for example, of a polyurethane-urea (U) and a polyacrylate[14]. This was followed by casting a film and crosslinking. The polyacrylate was essentially crosslinked through sulfur and double bonds by a free radical process. The urethane polymer was crosslinked thermally by reaction with triols.

This system was particularly chosen for two reasons: (1) the difference in crosslinking mechanism of the two polymers and (2) the ability of the urethane network to be selectively hydrolyzed at its ether linkages. Thus, films of the IPN were hydrolyzed with dilute hydrochloric acid, leaving still an integral polymer film. Weight loss and infrared spectroscopy showed that almost all of the urethane component was hydrolyzed and separated. This chemical proof suggested strongly that a considerable part of the individual networks were not chemically bound to each other, but indeed topologically interlocked. Subsequent work[6,35] showed that these materials appear to exhibit two distinct T_g's when studied by a Vibron viscoelastometer, but only one T_g could be resolved by differential scanning calorimetry (DSC) measurements[*] (cf. also Fig. 2).

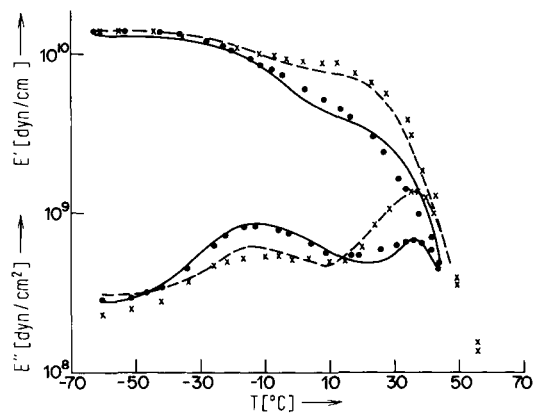


Fig. 2. Real (E') and loss (E'') moduli *vs.* temperature (T) for IPN of poly(urethane-urea) (U) and polyacrylate (H). ●●● U/H = 50/50, × × × U/H = 30/70, solid lines represent predictions based on theoretical models.

[*] A brief comment concerning the glass transition behavior of blends of polymers is warranted at this point. If two polymers combine to form a single phase mixture, one fairly sharp T_g, intermediate in temperature to the T_g's of the component polymers, would be expected. If separate, distinct phases occur, each phase should exhibit its own independent thermal response. Thus, two T_g's corresponding to the T_g's of the component polymers should occur. Any phase mixing which could occur at the phase boundaries would be expected to shift the component polymer T_g's inwards, *i.e.* towards each other until, if the domain size becomes small enough, one broad T_g would occur. Complete phase mixing would be indicated by one sharp T_g.

Electron microscopy of these IPN's (Fig. 3) also indicates their two-phase nature, with the polyacrylate as the continuous phase and the polyurethane the dispersed phase at concentrations as high as 70 % U, where a phase inversion apparently occurs.

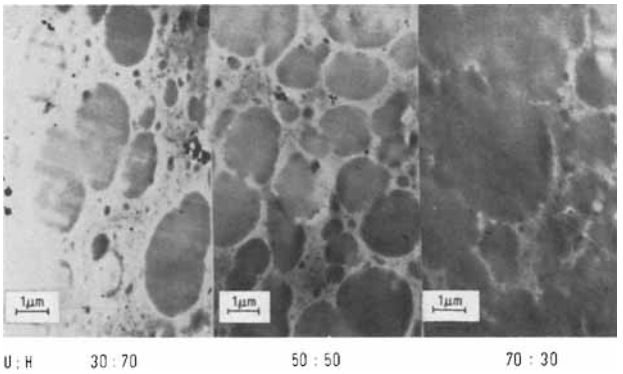


Fig. 3. Electron micrographs of IPN's of a poly(urethane-urea) (dark phase) (U) and a polyacrylate (H).

The domain sizes are of the order of magnitude of a micron to 1000 Å, *i.e.* about a factor of ten smaller than the latex particles in the original latices. These are the earliest examples of *Kato*'s osmium tetroxide staining technique[36] being used on IPN's. In this technique, osmium tetroxide preferentially stains one of the polymers (in this case the polyurethane), causing it to appear as the darker phase in the electron micrograph, due to the presence of the heavy metal atoms. The mechanical behavior of these IPN's substantiates this phase inversion. The fact that only one broad T_g was observed calorimetrically suggests that phase separation was not complete and that some interpenetration must take place at the phase boundaries.

Other examples of such LIPN's have been prepared[14]; since most of these consist of two different elastomeric networks, they have also been referred to as interpenetrating elastomeric networks (IEN).

Sperling et al.[37–40] prepared, as early as 1969, a series of SIPN's. While the SIPN made from poly(ethyl acrylate) and polystyrene[37] exhibited two distinct T_g's somewhat shifted towards one another, the SIPN, made from the polymers with zero heat of mixing, poly(ethyl acrylate) and poly(methyl methacrylate), exhibited only one broadened T_g[38]. In view of the further mechanical, solubility and thermal studies there is little doubt that these results can only be satisfactorily explained on the basis of interpenetration and not simply chain transfer crosslinking. These materials were synthesized to provide rather more or less compatible polymer blends, whose phases would remain finely divided without the need for further mechanical mixing.

Electron microscopic studies of the SIPN morphology[41] substantiated this behavior. For the 50 : 50 poly(ethyl acrylate) polystyrene IPN, the poly(ethyl acrylate) component contained *ca.* 1 % butadiene as a comonomer to facilitate osmium tetroxide staining. Figure 4 exhibits the complex morphology of this system. The cell walls are mainly poly(ethyl acrylate), the inner cell domains being mainly polystyrene. A fine structure is observed mainly within the cell walls. Sometimes, but not as frequently, the fine structure is observed inside the cells.

In the first case polystyrene domains are pervading the poly(ethyl acrylate) walls, whereas in the latter, poly(ethyl acrylate) particles are pervading the polystyrene cells. The sizes of the cells are approximately 1000 Å. The poly(ethyl acrylate) and the polystyrene microstructures are of the order of 100 Å. Although the cells are irregularly shaped, they exhibit a certain orientation which coincides with the radiation direction of polymerization.

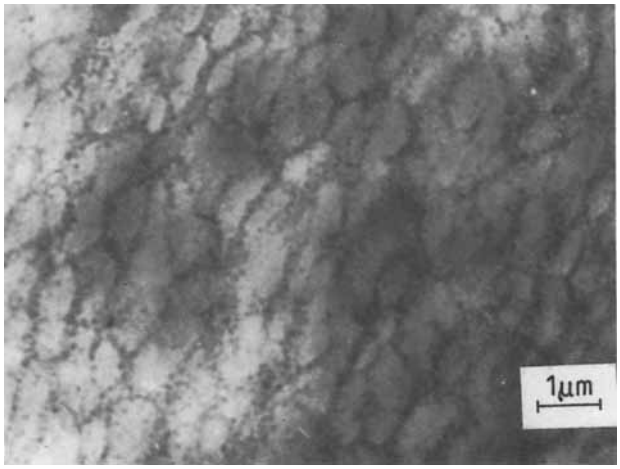


Fig. 4. Electron micrograph of a 50:50 poly(ethyl acrylate)/polystyrene IPN. Note appearance of a cellular structure and a fine structure within the cell walls.

The electron micrograph of the more compatible system, poly(ethyl acrylate) and poly(methyl methacrylate) 75:25 is shown in Figure 5. It can be seen that this material, while still exhibiting two phases, has only the fine structure, of the order of magnitude of 100 Å.

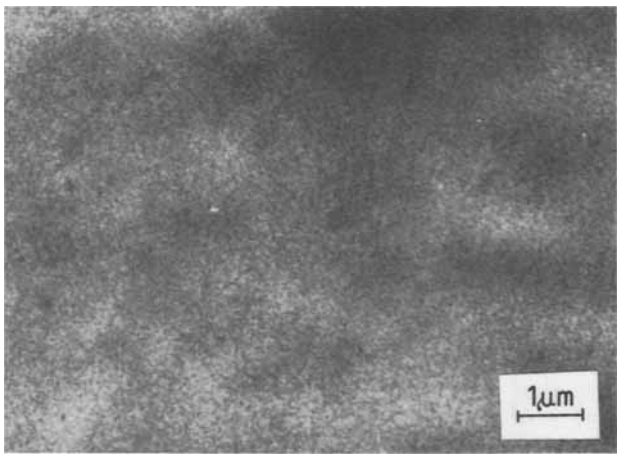


Fig. 5. Electron micrograph of a 75:25 poly(ethyl acrylate)/poly(methyl methacrylate) IPN. No cellular structure was detected for this composition; only the fine structure is present.

Presumably, the sequential mode of synthesis of these SIPN's provides the electron microscopic "cellular" and "fine" structures. Similarly, the underlying size of the latices in our IPN's and the difficulty of overcoming both the surface and bulk forces keeping the particles apart prevent a uniform morphology with very small domain sizes up to submolecular dimensions. To overcome this, both *Sperling* and his coworkers and our group developed the simultaneous interpenetrating networks (SIN). This technique, along with some other new developments, shall be discussed in the following sections.

3. Simultaneous Interpenetrating Networks

The method employed by us[16–23,42–45] involves mixing the linear prepolymers, together with crosslinking agents and catalysts (with or without solvent) casting films and/or sheets, and subsequently thermally curing them *in situ*. Care was taken to employ a step reaction with a chain reaction, or two step reactions which did not interfere with each other. In this fashion, binary SIN's composed of polyurethane-epoxy[18,42], polyurethane-unsaturated polyester[42], and polyurethane-polyacrylate[16,17,19,43] were formed. In all cases, one component was a rubbery polymer and the other a glassy one. This not only provided for the mutual reinforcement described earlier (*i. e.* either a high impact plastic or a reinforced elastomer), but also facilitated a phase analysis by glass transition measurements since this depends on the component polymers having widely separated T_g's.

The rubbery polymer was, in all cases, a polyurethane. It was made by the two-step prepolymer technique in which an isocyanate-terminated urethane prepolymer was first synthesized by reacting a hydroxyl-terminated low molecular weight polyether or polyester (polyol), usually difunctional, but in some cases multi-functional with a diisocyanate. This low molecular weight prepolymer (usually $\bar{M} \approx 500$—2000) was then chain extended and crosslinked simultaneously by reacting with short chain diols and triols, catalyzed by organotin compounds. Thus, a wide variety of polyurethanes were employed by varying the nature of the polyols, isocyanates, and chain extenders. This allowed determination of structure-property relationships.

The epoxy was also a liquid prepolymer or monomer and was cured with 2,4,6-tris(dimethylaminomethyl)phenol (DMP-30), a tertiary amine which would be non-reactive with the isocyanate.

The unsaturated polyester was a low molecular weight ($\bar{M}$ *ca.* 2000) polyester containing some unsaturation which was crosslinked with styrene *via* a free radical process, again non-reactive with the urethane component. The polyacrylate was also a fairly low molecular weight polymer ($\approx$ 10000) which was crosslinked with a butylated melamine-formaldehyde resin *via* pendant hydroxyls (it was a copolymer of butyl methacrylate, methacrylic acid, styrene, and hydroxyethyl methacrylate). In this case the isocyanate-terminated prepolymer had to be blocked by reacting with 2-butanoneoxime, in order to render it non-reactive with the pendant hydroxyls on the polyacrylate, and thus prevent grafting between the component polymers. Deblocking occurred only slowly at the curing temperatures, so that the pendant hydroxyls all reacted before the isocyanate deblocked.

IPN's were formed by mixing the urethane prepolymer (either in solution or in bulk), together with its chain extenders and crosslinking agents, with either the epoxy, polyacrylate, or polyester together with their respective crosslinking agents, casting films or molding sheets, and thermally curing them at *ca.* 100 °C overnight. All the IPN's exhibited single phase

morphologies, as evidenced by the presence of one intermediate T_g measured calorimetrically. Electron microscopic studies of the polyurethane-polyacrylate IPN's (Fig. 6 to 8) substantiate these results. No microstructure at all can be seen. Some granularity may be noted in the high polyurethane IPN (Fig. 8), but this is not evidence of phase separation since it occurs in the greatest amount in the 100 % polyurethane so is probably not a characteristic of the IPN's themselves.

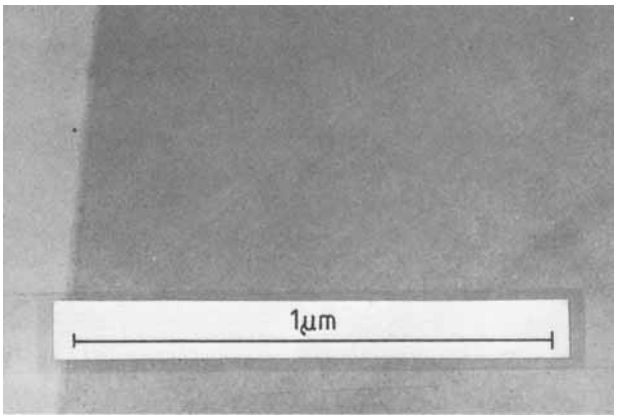


Fig. 6. Electron micrograph of a single-phase polyurethane (PU)/-polyacrylate (PA) IPN. PU/PA = 25/75.

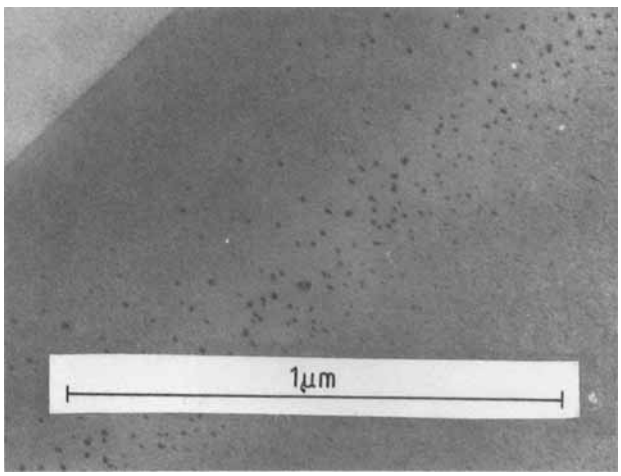


Fig. 7. Electron micrograph of a 50:50 PU/PA single-phase IPN.

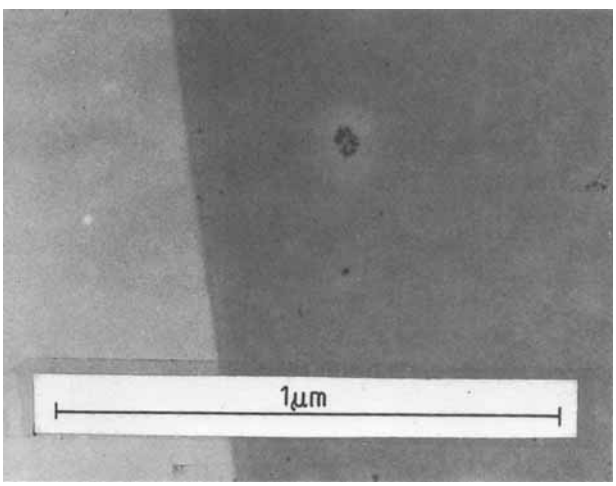


Fig. 8. Electron micrograph of a 75/25 PU/PA single-phase IPN.

The physical and mechanical properties of these IPN's showed interesting and remarkable trends. Maxima in tensile strengths *vs.* IPN composition which were significantly higher than the tensile strengths of the component polymers occurred for most of the above SIN's. Typical results for the polyurethane-epoxy IPN are shown in Figure 9.

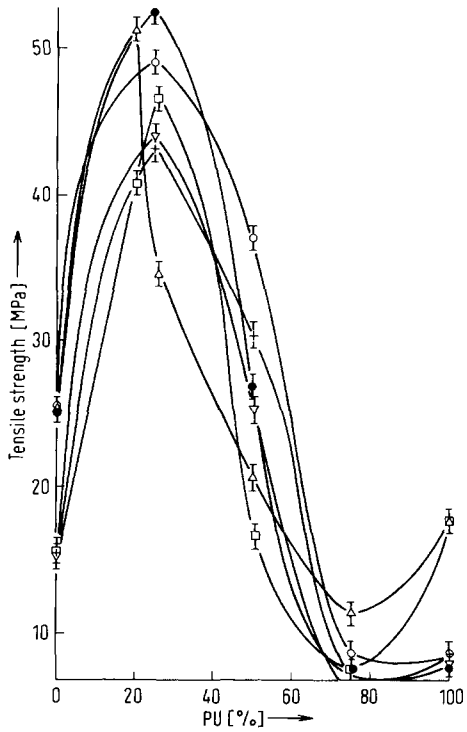


Fig. 9. Tensile strengths *vs.* composition for polyurethane/-epoxy IPN's. The several curves represent IPN's composed of varying polyurethanes and epoxies. Note the behavior is the same in all cases.

In many cases, minima also occurred. The maxima were attributed to an increase in crosslink density due to interpenetration, since it is well known that the tensile strength of a crosslinked rubber goes through a maximum as the crosslink density increases. The minima were attributed to initial weakening of the strong hydrogen bonding present in the polyurethanes by the interpenetrating chains of the second polymer. Crosslinking between the two polymers was postulated to be another possibility for maxima in the strength properties, since this possibility did exist with these IPN's. The melamine-formaldehyde resin could conceivably react with the hydroxyl-terminated chain extenders of the polyurethane, in the case of the polyacrylate IPN's. For the unsaturated polyester IPN's, reaction between the isocyanate-terminated prepolymer and the terminal hydroxyl and/or carboxyl groups of the polyester is certainly possible. Some of the epoxide polymers studied contained some pendant hydroxyls which could react with the isocyanate. In addition, the epoxide itself could react with the isocyanate. However, under the curing conditions employed (catalyst, temperature, *etc.*) the authors speculated that this "inter-reaction" would be minimal. Infrared studies seem to support this view[16, 17]. Other properties which showed enhancement were the thermal resistance (as evidenced by thermogravimetric analysis) and the impact strength.

The method employed by *Sperling et al.*[46] to form the SIN's involved simultaneously synthesizing crosslinked epox-

ide polymers and *n*-butyl acrylate polymers. A two-phase morphology resulted, with the dispersed rubber (poly(*n*-butyl acrylate)) domains being of the order of 0.1—0.2 μ in size. The actual dimensions of the dispersed phase, and the extent of molecular mixing (interpenetration) between the two networks was found to depend on the relative rates of polymerization, or the gelation time. The minimum domain size and therefore greatest amount of interpenetration occurred when the closest approach to simultaneity was attained. Spherical, rather than elongated rubber domains yielded the greatest toughening of the epoxy when the domains were smaller than optimum.

4. Interpenetrating Latex Polymer Networks

Another type of latex IPN, different in nature from those we synthesized[6,17,15,37,35] and discussed in Section 3, are those of *Sperling et al.*[47–50], which resulted in semicompatible IPN's. This synthesis consisted of making a seed latex of crosslinked polymer A, and then introducing monomer B (containing crosslinking agent), followed by a second emulsion polymerization. Films were formed either by coagulating or drying the IPN latex. Numerous polymer combinations were studied, including poly(vinyl chloride)/poly(butadiene-acrylonitrile)[49], and a variety of methacrylic/acrylic combinations, such as poly(ethyl methacrylate)/poly(*n*-butyl acrylate)[50]. The interesting characteristic of these IPN's is that they display glass transitions that are broadened and, in some cases, span the entire temperature range between the two component polymer transitions. As mentioned earlier, this type of behavior suggests semi-compatibility, *i.e.* much less phase separation between the polymers. It does not imply complete phase mixing, as only one sharp T_g would then be observed. The morphology suggested was a core-shell structure[51], where the polymer A core gradually becomes enriched in polymer B on going from the center of the latex particle to the surface.

The broadened glass transition behavior of these IPN's has led to their study as noise and vibration damping coatings. When a material is in its glass transition region, the mechanical damping factor, or dissipation factor, tan δ, (as obtained from a dynamic mechanical relaxation measurement) goes through a maximum. The interest in these IPN's is due to the fact that their glass transition extends over a wide temperature range, which means that they would be useful damping materials not just over a short temperature span (the usual transition of polymers), but over a wide range of temperatures.

5. Incompatible Polyurethane Simultaneous Interpenetrating Networks

We recently synthesized a series of SIN's[20,22,44,45,52,53], with a polyurethane as the rubber component, which are characterized by a heterophase morphology similar to the LIPN's[6,17,15,34,35], as opposed to the single phase nature of the previously described SIN's[8,16–19,43]. The factors which distinguish these SIN's from the previous single phase ones are the nature and the crosslinking mechanism of the glassy polymer. Two polymers were selected as the glassy ones: polystyrene (crosslinked with divinylbenzene), and poly(methylmethacrylate) crosslinked with trimethylolpropane trimethacrylate. The solubility parameters of these polymers (which reflects their compatibilities) were farther from the polyurethane than those of the previously discussed glassy polymers used in the compatible SIN's. In addition, practically no chance for reaction between the polymers in these SIN's existed, as they did in the case of the earlier ones. Any interreacting, or grafting, between the component polymers would help to compatibilize them.

The polyurethane—poly(methyl methacrylate) SIN's exhibited less phase separation than did the polystyrene SIN's (as would be expected from a solubility parameter study) as evidenced by the relative shifts in T_g's (measured by dynamic mechanical spectroscopy and calorimetry) as well as electron microscopy (Fig. 10 and 11). The size of the dispersed domains is much smaller for the poly(methylmethacrylate) IPN's than the polystyrene. Interpenetration was postulated to occur at the phase boundaries.

The effect of interpenetration on the morphology, as well as properties, was deduced in this study. Pseudo-IPN's (in which only one component was crosslinked) and linear blends were formed by omitting the appropriate crosslinking agent.

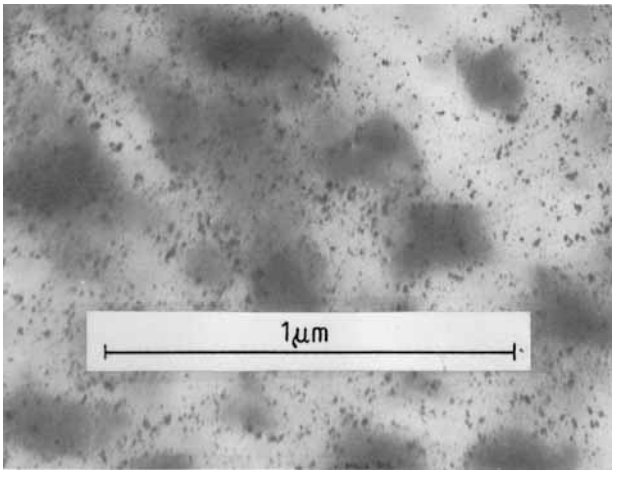


Fig. 10. Electron micrograph of polyurethane/-polystyrene Simultaneous Interpenetrating Networks: Polyurethane/polystyrene in the ratio 75:25.

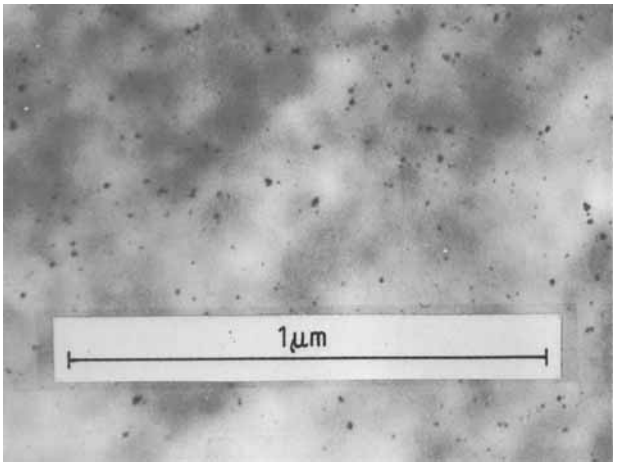


Fig. 11. Electron micrograph of polyurethane/poly(methyl methacrylate) simultaneous interpenetrating networks: polyurethane/poly(methylmethacrylate) in the ratio 75:25.

Both electron microscopy and glass transition behavior showed that the extent of phase separation was greater in the case of the pseudo-IPN's and linear blends. This indicated the role of permanent interpenetration on reducing phase separation by reducing the domain size of the dispersed phase. Pseudo-IPN's and linear blends could not limit phase separation since no topological constraints exist. The polymers can simply "unthread" and phase separate without breaking covalent bonds. The ultimate properties also reflect this behavior. Significant enhancement in tensile strength occurred with these IPN's, much greater than that for the pseudo-IPN's or linear blends. In this case, it is not the increased crosslink density which can explain this phenomenon, but the mutual glassy-rubbery reinforcement effect. Interpenetration serves to decrease the domain size and provide adhesion between the phases, thereby increasing the enhancement effect.

The densities of these IPN's[45], as measured hydrostatically, were increased, due presumably to the partial mixing of the component networks. This density increase agreed well with the specific volume hypothesis of *Kwei*[54] for a compatible polymer pair.

6. Current Studies

Sperling et al. are presently actively pursuing IPN's based on castor oil[55, 56] and those consisting of poly(styrene-butadiene)/polystyrene[57, 58].

The latter IPN's were prepared by the sequential technique. The polymer synthesized first was varied as well as the level of crosslinking. Pseudo-IPS's were also made. Electron microscopic investigations showed that the polymer synthesized first formed the more continuous phase and tended to control the morphology. The second polymer formed a cellular structure whose size was determined principally by the degree of crosslinking of polymer A, with an increase in crosslinking producing a finer structure. The coarsest structure was with the pseudo-IPN's, in agreement with our observations[44]. Thus, the two principal groups studying IPN's both agree on this very important concept, *i. e.* that interpenetration does affect the morphology and can somewhat "compatibilize" incompatible polymers. The mechanical behavior of these polymers was also studied[58]. Dynamic mechanical behavior showed two distinct T_g's in agreement with the electron microscopic data. These IPN's produced toughened materials, similar to our SIN's[20, 22], as evidenced by tensile and impact tests. Crazing appeared to be the principal toughening mechanism, and an optimum degree of toughness was obtained at an intermediate level of crosslinking of the polymer A component.

The castor oil based IPN's consisted of a polyurethane and either polystyrene or poly(methylmethacrylate). They were made again by the sequential technique, in which polyurethanes based on castor oil were swollen with the vinyl monomer. These IPN's were produced in order to develop a high impact material in which the rigid vinyl polymers were toughened by the rubbery polyurethane, in a fashion similar to our heterophase SIN's (see Section 3). The unique feature of these IPN's is that the elastomeric phase was based on a non-petroleum product, a facet of obvious importance in the light of today's energy shortage. The castor oil was polymerized both by sulfur, through the unsaturation on the molecule, or with diisocyanates, to form a polyurethane. This polymer was then swollen with the vinyl monomer, plus crosslinker and catalyst, and polymerized. One problem with this IPN is that undoubtedly much grafting occurs between the component polymers, since castor oil is an unsaturated material and subject to attack by the free radicals from the vinyl polymerization. The authors contend, however, that the amount of interpenetration is greater than the amount of grafting. Electron microscopy revealed a two phase morphology. The domain size ranged from 300 to 500 Å. Either increasing the castor oil content or decreasing its crosslink density caused the domain size of the dispersed polystyrene to increase. Measurements with a torsional pendulum gave separate, distinct T_g's for the component polymers. The IPN's were all clear and tough. Depending on compositions, either reinforced elastomers or impact resistant plastics resulted.

Our group is presently pursuing several avenues. In order to determine the mechanism behind the single phase morphology of the previously described polyurethane/polyacrylate SIN's, pseudo-IPN's and linear blends were prepared[59]. In addition, a polyacrylate very similar to the one discussed earlier, was prepared which crosslinked by a free radical process. In this manner, the possibilities of grafting which existed with the earlier SIN's were removed. The morphologies in all cases, as determined by differential scanning calorimetry, were heterophase. In all cases, two T_g's corresponding to the T_g's of the component polymers, resulted. They were shifted inwards, indicating some interpenetration, most likely at the phase boundaries. This suggests that grafting did occur in the earlier IPN's and that it played an important role in compatibilizing the polymers. The effect of polymerization kinetics on the morphology was determined. It was found that interpenetration increased as the reaction rates increased, and reached a maximum when the gel time of both polymers was the same, in agreement with *Sperling*'s results[57]. It was postulated that this was most likely due to the fact that increasing the reaction rate lowers the diffusion time allowed for phase separation. The initial prepolymer mixture is single phase, since the molecular weights are low enough to allow complete mixing. As the polymers are chain extended and crosslinked, they phase separate due to their thermodynamic incompatibility. This phase separation is naturally diffusion controlled and thus requires time. If the curing reactions are accelerated, less time will be available for diffusion and subsequent phase separation. When fully crosslinked, further phase separation cannot take place due to topological restraints imposed by the crosslinking of the component polymers, *i. e.* "disentangling" of the chains cannot occur without rupturing covalent bonds. Thus, further crosslinking would be expected to yield less phase separation. Significant enhancements in the tensile strengths resulted for the IPN's, but not for the pseudo-IPN's or linear blends. This reflects the higher level of mixing most likely present in the full IPN's (both polymers crosslinked).

Our team is also studying the surface, adhesive and barrier properties of polyurethane-epoxy SIN's[60]. Single phase morphologies were again found by glass transition analysis for these SIN's. They exhibited significantly enhanced adhesive properties, such as lap shear strength and peel strength (Fig. 12 and 13).

Maxima in these properties as a function of composition occurred at the same place as the maximum in tensile strength (Fig. 14).

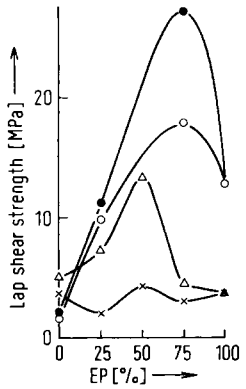


Fig. 12. Lap shear strength *vs.* composition for a polyurethane/epoxy IPN.

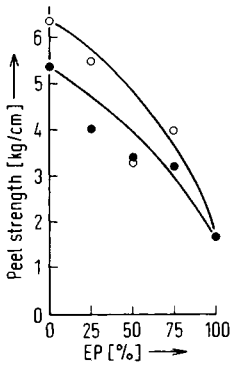


Fig. 13. Peel strength *vs.* composition for a polyurethane/epoxy IPN.

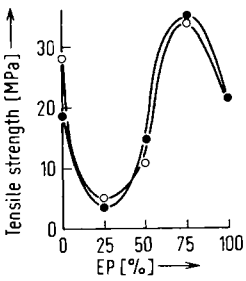


Fig. 14. Tensile strength *vs.* composition for a polyurethane/epoxy IPN.

Likewise, minima in critical surface tension, as determined by measuring the contact angles of a series of liquids, occurred at the same composition (Fig. 15).

This is consistent with the adhesive results since low critical surface tensions indicate higher wettability of these materials. This, together with the tensile properties, suggests that the failure in the peel and lap shear tests was both adhesive and cohesive. The barrier properties were investigated by determination of the water vapor permeabilities of SIN coatings (Fig. 16).

These results were indicative of a single phase morphology, in agreement with the glass transition results.

Finally, we have discovered an acrylic polymer that is extremely compatible with polyurethanes. A series of IPN's, pseudo-IPN's, and linear blends is being prepared.

A new group has recently started investigations on IPN systems[61]. They have produced SIPN's of a polyurethane and polystyrene similar in chemistry to our SIN's[20]. They found, for the first time, a third T_g, (as measured by gas chromatography) between the component T_g's, suggesting a three phase morphology, the two component polymers plus

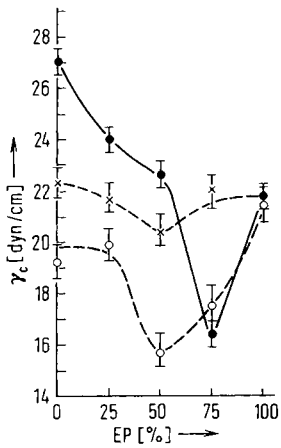


Fig. 15. Critical surface tension *vs.* composition for a polyurethane/epoxy IPN.

an interpenetrating region substantial enough to possess its own T_g. They also developed a thermodynamic method of obtaining the crosslink density (an indication of interpenetration) of this IPN from the measured retention volume in gas chromatography with the IPN as the column packing material. For the first time, theoretical calculations regarding the compatibilities of the component polymers were made.

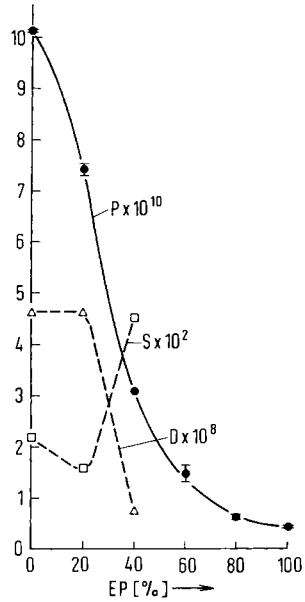


Fig. 16. Water-vapor permeabilities of a polyurethane/epoxy IPN. P[g·cm/cm^2·s·(cm Hg)] is the permeability coefficient; S[g/cm^3·(cm Hg)] is the solubility coefficient; D[cm^2/s] is the diffusion coefficient.

7. Unsolved Problems and Future Studies

How much interpenetration is really occurring? All investigations to date assume that single phase morphologies imply

interpenetration, *i.e.* entanglement of the chains of both polymers, similar to that which occurs in homopolymers. But this is not necessarily the case. A technique must be devised to "see" the chains. Electron microscopy is not yet a sensitive enough probe for polymers. Catenanes, or threaded macrocycles naturally occurring in cyclic DNA, have been "seen" electron microscopically[62], since DNA is a thick enough molecule to be resolved by the electron microscope. No such evidence has been presented for IPN's.

Another problem is the extent of grafting occurring between the polymers. Only one attempt has been made to demonstrate the absence of covalent bonds between the polymers[14]. For true topological interpenetration to occur, there must be no covalent bonds between the polymers. Most of the investigations to-date have tried to minimize grafting by the appropriate selection of polymers and crosslinking mechanisms. However, positive proof of the absence of grafting has not been given.

All IPN's to-date have been two-component. Multi-component IPN's would be expected to exhibit highly complex morphologies and should present a very interesting study. Fascinating physical properties should be expected from such complex networks.

One technique for the formation of IPN's which has not been attempted is the growing of both polymers from a single substrate, followed by cleavage of the bonds between them. This would insure that the chains of both polymers would be in close proximity during polymerization and increase the chance of interpenetration. Such a technique has been used successfully for the synthesis of threaded macrocycles, or catenanes[63, 64].

Polymers are useful as materials in forms other than plastics, rubbers, and coatings, *e.g.* as foams. Preliminary interpenetrating foams made by *Frisch* (unpublished) have shown excellent properties[65]. One interesting application of this could be in reducing the flammability of rigid polyurethane foams, the biggest hindrance to the widespread use of these materials in insulation. Most of the techniques for reducing flammability severely reduce the physical and mechanical properties of these foams. IPN foams could conceivably be made in which one polymer is the base network, and the other contains fire and smoke reducing elements, such as phosphorus and halogens. This could conceivably result in less of a sacrifice in properties.

Further studies of the barrier properties of IPN's are necessary. This could be an extremely useful probe in determining the topology of these networks. Very little work on permeabilities of composite structures has been performed.

Lastly, and undoubtedly the most difficult task, are the theoretical considerations. Statistical mechanical calculations to predict the topology could prove quite useful. Such calculations have been made for catenanes[9]. An extension of these calculations for the polymer situation should be possible. They must, of course, take into account the compatibility problem, as well as the statistical problem. The former problem has not been solved satisfactorily for simple polymer blends, and should thus prove all the more complex for IPN's. If this problem is solved, the morphologies and properties of IPN's of any polymer pairs could be predicted.

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The Realities of Extended Homoaromaticity

By Leo A. Paquette[*]

Homoaromaticity has been the subject of many investigations and continues to remain an extraordinarily rich area of chemistry. Quantitative experimental evaluation of the level of long range delocalization and assessment of interactions in molecules having two or more insulating atoms, together with various theoretical estimates of energies and geometries, are areas currently being examined. The primary intention of this review is to provide a critical up-to-date survey of relevant spectral and structural data, as well as an analysis of the many reactions believed to involve generation of homoaromatic ions. Extensively discussed are mono-, bis-, and trishomoaromatic systems arranged on the basis of their cationic, anionic, or uncharged nature. Presentation of these individualized segments is preceded by a brief analysis of homoaromatic overlap.

1. Introduction

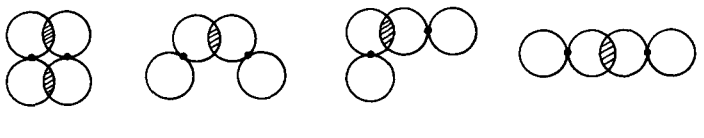
The concept of homoaromaticity was advanced by *Saul Winstein* almost 20 years ago to account for the unusual solvolytic behavior of the bicyclo[3.1.0]hex-3-yl cation[1]. The hypothesis has proven inspirational to many chemists and has had the undeniable effect of directing much experimental and theoretical attention to this field[2]. Major advances continue to be made, chiefly because of the extraordinary richness of the molecular architecture to which the theory may in principle be applied. Extensive discussion and debate have accompanied these developments. In part this has been due to an increasing sophistication in our theoretical understanding of the subject. But the varied success encountered in the observation of homoconjugative delocalization within certain ions and molecules of predesigned structure has also generated some consternation. At issue is the rather qualitative question: how extensively can π-electron delocalization in $(4n+2)$ conjugated polyenes be interrupted by one or more saturated atoms (sp^3 centers) with continued maintenance of some form of ring current? The primary intention of this review is to survey somewhat critically the major new developments in homoaromaticity with particular emphasis on higher order (bis, tris, *etc.*) phenomena and to address the above question in the light of current thinking.

2. Homoaromatic Orbital Overlap

We herein refer to the all too familiar parallel alignment of π orbitals so characteristic of aromatic systems (cf. *A*) as pp-π overlap. This combination possesses a node in the plane of the bond axis, has angular momentum about this axis, and is doubly degenerate. When a $(4n+2)$ cyclic array of these orbitals is fractured to accommodate an sp^3-hybridized center, electron delocalization can only be maintained if the two flanking π-atomic orbitals become canted more or less as in *B*. For obvious reasons, overlap becomes restricted to single lobes, the boundaries of which are limited to that surface of the molecule opposite to the bridging atom. The extent of interpenetration of the opposed p_z orbitals in *B* can be expected to depend heavily upon their mutual orientation and the internuclear distance separating the trigonal atoms. The net level of homoaromatic delocalization will be linked directly to the resultant overlap integral and the degree to which these atomic orbitals contribute to the molecular wave

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functions comprising the ground state configuration of the molecule. The situation prevailing for a specific compound where known will be discussed in the individual sections which follow.

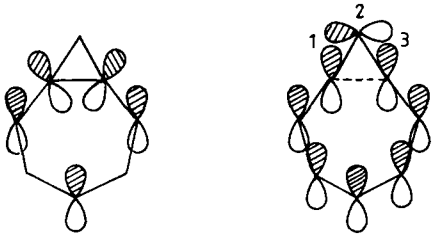


A B C D

Increasing σ Contribution →

The orbital overlap in *B* lies intermediate between pp-π and pp-σ. Further progressive alteration of this spatial orientation can lead to *C* and *D*. Anticipated by such changes is a further diminution in the level of π interaction and a concomitant increase in σ contributions to the bond energy (a fixed separation of atom pairs is assumed). The consequences of perpendicular pπ orbital arrangement as given by *C* has been examined in very few situations[3–5]. At the far extreme, the combination of parallel colinear atomic pπ orbitals depicted in *D* is seen to be cylindrically symmetrical about the bond axis, to lack angular momentum, and to be nondegenerate. The commonly prevailing π contributions to p orbital interaction are completely factored out in *D* and examination of pure pp-σ interactive behavior should be possible. However, molecules having this interesting feature are currently unknown (with the possible exception of diazabicyclo-[2.2.2]octane[6])[7], although the transition states of many reactions (Diels-Alder, *etc.*) are believed to encompass approach of a pair of pπ reactants in such sigmoid fashion. While *C* and *D* do not fall strictly within the confines established for homoaromatic interaction, they are briefly mentioned here for completeness.

Considerable theoretical effort has been expended in attempts to assess the energetics of homoaromatic interaction. Both *Hehre*[8] and *Haddon*[9] have opted not to view the external methylene carbon as an isolated entity, but to consider it instead as part of a cyclopropane ring to which a linear segment is attached. In these terms, the monohomotropylium cation can be considered stabilized by appropriate interaction of the HOMO Walsh cyclopropane orbital and the LUMO



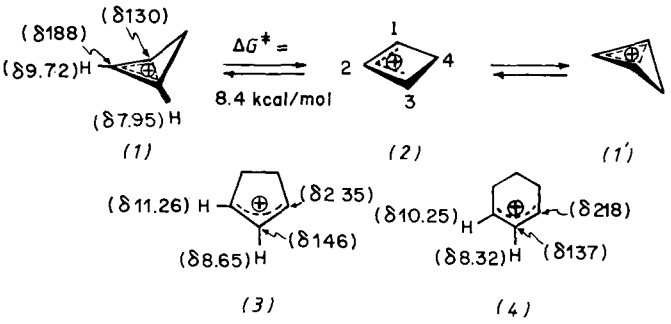
E *F*

of pentadienyl as in *E*. However, this type of interaction is seemingly valid only if the cyclopropane ring is closed (the allowable bond length has never been specified) and such is unlikely to be the case. For this reason, the Möbius representation *F* which utilizes the outer electrons of the C-2 methylene for back-donation to the pentadienyl moiety in order to lengthen the C-1—C-3 distance was in vogue briefly, although later discarded[10]. *Jorgensen* has utilized extended Hückel, MINDO/3, and perturbation theory calculations to arrive at rather quantitative estimates of the energetic importance of homoaromatic overlap in certain select systems[11].

3. Monohomoaromatic Systems

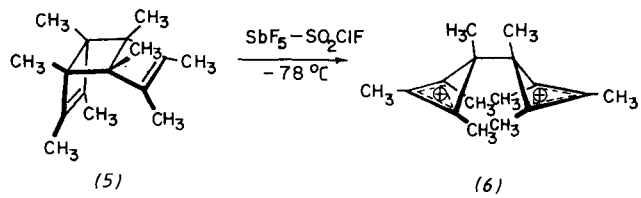
3.1. Cations

Monohomocyclopropenium cations are the simplest possible homoaromatic systems. Experimental support for the existence of 1,3 overlap as in *(1)* has been derived exclusively from ^{1}H- and ^{13}C-NMR data[12,13]. In particular, the pronounced upfield shifting of C-1 and C-3 as well as H-1 and H-3 (relative to that in *(3)* and *(4)* where the ordering is actually reversed) has been interpreted as indicative of homoconjugative interaction which shifts greater positive charge to C-2. Also, the methylene protons exhibit a temperature dependence consistent with a nonplanar conformation, although the small Δδ which separates them would seem to indicate that the extent of ring puckering is small[13]. This conclusion is supported by the experimentally determined

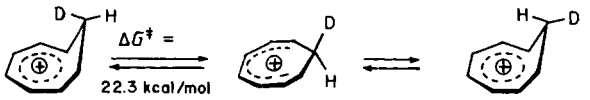


8.4 kcal/mol barrier to ring flipping, the level of which compares closely with theoretical estimates[11]. Despite this convincing evidence for electronic delocalization, it is unfortunate that no structural (*e.g.* X-ray) data are available to provide irrefutable information concerning the C-1—C-3 distance (calcd 1.739 Å)[11], the C-2—C-1—C-4 angle (calcd 148.3°)[11], and other important molecular dimensions.

Some measure of the driving force underlying the generation of these cations is provided by the overwhelming tendency of *(5)* to undergo clean two-electron oxidative ring opening in SbF_5-SO_2ClF with generation of *(6)*[14].

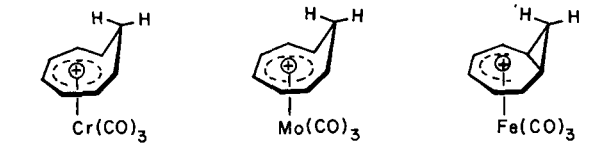


Developments in homotropylium ion chemistry began with *Pettit*'s early observation that treatment of cyclooctatetraene with concentrated H_2SO_4 or with $SbCl_5$ and HCl in nitromethane generated a cation with an unusual ^{1}H-NMR spectrum[15]. Subsequent work in *Winstein*'s laboratory showed the available



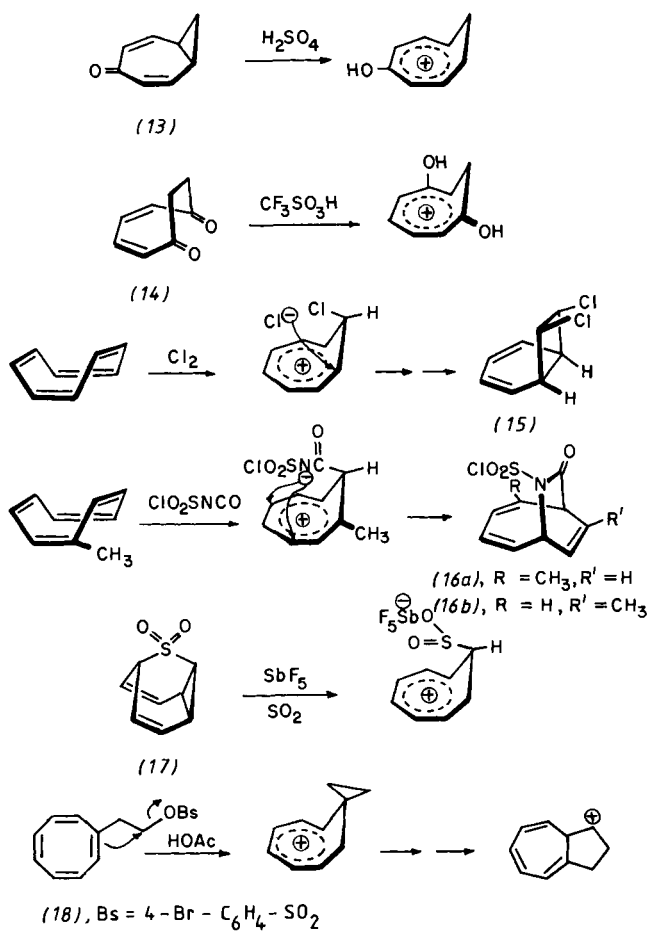
(7) (8) (9)

data to be best accommodated by a delocalized six electron structure where the prevailing ring current deshields the *exo* proton and shields the *endo* one ($\Delta\delta = 5.8$ ppm)[16]. Through use of D_2SO_4 below -15 °C, it could be demonstrated that D^+ attacks predominantly (80 %) from a position within the interior of the cyclooctatetraene tub conformation to give *(7)*, which on warming suffers *exo/endo* equilibration presumably *via* the planar cation *(8)* ($\Delta G^{\neq} = 22.3$ kcal/mol)[17]. The suggestion that a ring current was present in *(7)* received further support from ^{13}C-NMR analysis[18] and demonstration that the *hexahapto*-carbonylmetal complexes *(10)* and *(11)* have similar $\Delta\delta$'s, but that the value for the η^4-tricarbonyliron complex *(12)* is significantly attenuated[16,19].



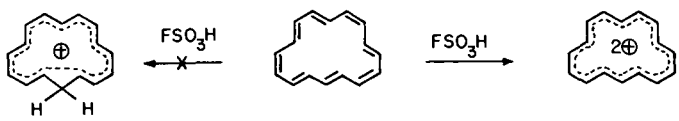
(10) (Δδ = 4.5) (11) (Δδ = 3.6) (12) (Δδ = 0.2)

The generation of homotropylium cations is an entirely general phenomenon which can arise upon (a) simple protonation of suitable acceptor molecules such as *(13)*[20] and



(13) (14) (15) (16a), R = CH3, R' = H (16b), R = H, R' = CH3 (17) (18), Bs = 4-Br-C6H4-SO2

(14)[21], (b) bonding of a biparticulate (*e.g.* Cl_2)[22] or uniparticulate electrophile (*e.g.* $ClSO_2NCO$) to cyclooctatetraene and its derivatives[23], (c) electrophilic attack upon a cyclic precursor such as *(17)*[24], and (d) solvolysis of an appropriate substrate such as *(18)*[25]. It is particularly ironic, therefore, that not one of the many known derivatives has been subjected to crystal structure analysis. Highly relevant questions concerning the internuclear distance separating C-1 from C-7, the angle of tilt of C-8 from the basal plane defined by the other seven carbon atoms, the bond lengths separating these centers, and the like, still remain unanswered. Until one or more definitive studies of this type are completed, we are forced to rely heavily upon the several theoretical estimates of π-electron distribution and homoconjugative interaction[8-11].



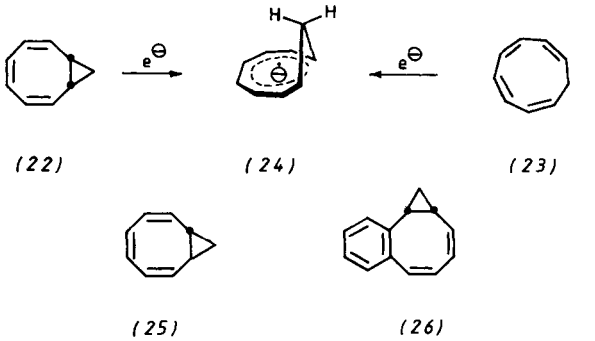
(20) (19) (21)

As one progressively increases the size of the homoaromatic ring, the level of resonance stabilization can be expected to decrease regularly to the point where it will eventually be offset by the strain energy caused by introduction of the homoconjugate bridge[8]. The upper limit in the maximum size of the ring may therefore be quite low. In the only experimental work to date which bears on this question, *Oth, Schröder*, and their coworkers have observed that dissolution of [16]annulene *(19)* in FSO_3H does not result in conventional protonation with the formation of *(20)*, but rather constitutes an oxidative method for generating the [16]annulenium dication *(21)*[26].

3.2. Anions

Because homocyclopentadienide anions are as yet unknown[27], the level of possible 6π6C delocalization attainable, if any, cannot be appreciated.

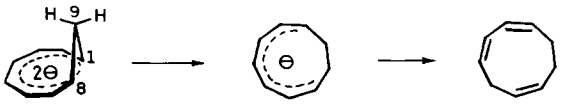
Upon reduction of *cis*-bicyclo[6.1.0]nonatriene *(22)*[28,29] or *cis*-cyclononatriene *(23)*[4,28], there is generated the radical anion *(24)* whose homoaromatic character has been inferred from ESR data and the contrasting behavior of the *trans* fused bicyclic *(25)*. The latter triene cannot undergo symmetry allowed disrotatory cyclopropane ring fission without engendering prohibitive strain energy. Electrochemical studies[30] on *(22)*, *(25)*, *(26)*, and structurally related molecules in



(22) (24) (23) (25) (26)

tetrahydrofuran and acetonitrile solution showed these hydrocarbons to deviate widely in their behavior from that exhibited by such 4*n* cyclic polyolefins as cyclooctatetraene[31] and [16]annulene[32] which are recognized to give rise to resonance stabilized reduction products. Both *(22)* and *(25)*, for example, undergo reduction with considerable difficulty, their respective waves appearing in the region characteristic of ordinary medium-ring trienes. Furthermore, none of the electron transfer processes are nernstian and cyclic voltammetry has revealed no reoxidizable product for any of the waves. It would appear therefore that at least in this instance electrochemistry does not serve as a suitable criterion for the assessment of developing homoaromatic character.

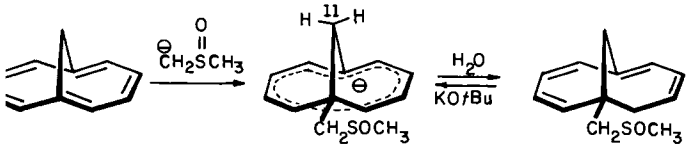
An early report by *Winstein* had indicated that further reduction of the radical anion *(24)* had provided the monohomocyclooctatetraene dianion *(27)*[28]. However, the original



(27) ($\Delta\delta = 2.6$) *(28)* *(29)*

spectral data given for *(27)* and the chemical reactivity ascribed to it are incongruous with more recent findings and must be questioned. The combined efforts of *Bates*[33] and *Paquette*[34] have generated convincing spectral evidence showing that *(27)* adopts the illustrated conformation where each of the original double bonds experiences some twisting to accommodate the homoconjugate bridge while maintaining maximum conjugative overlap. These dianions are much more basic than cyclooctatetraene dianions, being subject to ready protonation by ammonia at C-1 or C-8 with formation of cyclononatrienide anions *(28)*[34]. Subsequent quenching with a more electrophilic reagent permits isolation of 1,3,6-cyclononatriene derivatives [cf. *(29)*][34,35].

The only example of a possible monohomocyclononatetraenide anion *(31)* has been discovered by *Böll* while examining the nucleophilic addition of dimsyl anion to 1,6-meth-

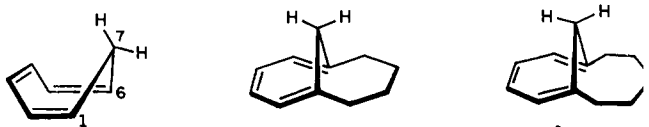


(30) *(31)* *(32)*

ano[10]annulene *(30)*[36]. As is often customary, the ^{1}H-NMR spectrum of *(31)* [which shows the C-11 protons to resonate at high field ($\delta = 0.18$)] was used as the sole indicator of extended cyclic delocalization.

3.3. Neutral Systems

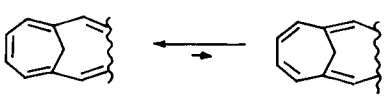
The question of whether cycloheptatriene and its derivatives are neutral homoaromatic molecules is one of long standing[37]. From electron diffraction studies[38], it is clear that the parent hydrocarbon adopts a boat conformation *(33)* in which the methylene group and the —CH=CH— structural element situated opposite to it are bent out of the basal plane (C-1, C-2, C-5, C-6). A cross section of *(33)* when viewed from this plane shows the C-1, C-6 p_z lobes to be geometrically related as in *B*. Since the internuclear distance and the mutual orientation of these two p orbitals relative to each other have been accurately determined, it is possible through use of vector analysis and Slater orbitals to calculate the extent of interpenetration as given by the overlap integral *S*[39]. These computations, which are facilitated by the C_s symmetry inherent in *(33)*, obviously require the two p_z orbi-



(33) ($\Delta\delta = 1.4$) *(34)* ($\Delta\delta = 2.22$) *(35)* ($\Delta\delta = 1.34$)

tals to possess the same phase in the overlap region (*i.e.*, a positive interaction) and the atomic orbital in question to be a dominant contributor to the molecular wave function. For *(33)*, the high degree of π bond localization supports the full occupancy, while its photoelectron spectrum[40] provides suitable evidence for the proper symmetry of these orbitals. The resultant magnitude of *S* (0.042) reveals that some overlap does occur at the periphery of those p_z lobes which are canted inward and that a finite level of homoaromatic interaction probably does exist. This level is obviously of low order (compare later) since the barrier to ring inversion, during which C-1 and C-6 overlap must suffer temporary disruption, is only *ca.* 6 kcal/mol[41,42].

Evidence that cycloheptatriene can support an induced diamagnetic ring current (at least when in a magnetic field) comes from direct analysis of its ^{1}H-NMR spectrum[41-43] and diamagnetic susceptibility data (the exaltation is 59% that of benzene)[44]. As *Childs* and *Pikulic* have noted[45], the entirely comparable differences in susceptibility exaltation between benzene (13.7) and the tropylium cation (17) *versus* 7-*tert*-butylcycloheptatriene (14.8) and the monohomotropylium cation (21) suggests that there is equal right on this basis to refer to the triene as a homobenzene. In bridged cycloheptatrienes such as *(34)* and *(35)*[46] the *syn* methylene bridge proton lies over the π electron cloud and is again subject to ring current shielding (the *anti* proton lies in the deshielding zone). The difference between the $\Delta\delta$ values of *(34)* and *(35)* may be related to the degree of "pinching" by the polymethylene bracket and the resultant alteration in the C-1—C-6 internuclear vector. In this connection, much experimental data have now been amassed showing that the cycloheptatriene part structure *G* is thermodynamically preferred over the 1,6-dimethylenecycloheptatriene part structure *H* in a rather diversified array of annulated molecules[47-51]. Although strain

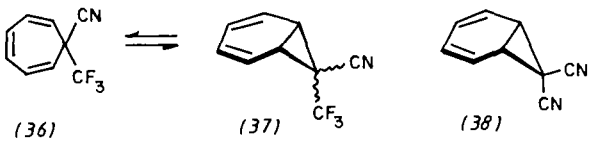


G *H*

effects may contribute in part to this phenomenon, one cannot avoid the conclusion that electronic factors exert a major impact upon the ground state stabilities.

The existence of *(33)* in equilibrium with an extremely small quantity of norcaradiene cannot be detected experimen-

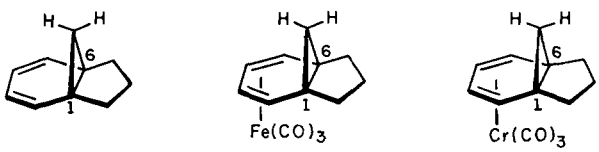
tally[52] but can be indirectly deduced from several of its chemical reactions[37]. Particularly dramatic is the shift in this equilibrium with C-7 substitution. For example, *(36)* and *(37)* have been isolated as separate entities (thereby eliminating these structures as possible resonance forms of a single homobenzene) and *(38)* is the preferred form of the 7,7-dicyano derivative[53]. *Hoffman*[54] and *Günther*[55] were the first to treat this question from the theoretical viewpoint by considering the interaction of the orbitals of the electron-withdrawing C-7 substituent with the cyclopropane Walsh orbitals in *(37)* and *(38)*. More recently, a direct relationship



(36) *(37)* *(38)*

between the stereochemistry (*syn vs anti*) and electronic character of the substituent and the position of equilibrium in monofunctionalized systems has been implicated[56]. Further experimental work is necessary before this issue is fully clarified.

One must be careful not to equate homoconjugative overlap in *(33)* with "norcaradiene-like character." Strictly speaking, homoconjugative interaction in the triene involves pπ orbitals (possibly admixed with low levels of s character) which are geometrically prohibited from entering into overlap as in *A* and which therefore can partake of interaction only on one surface as in *B*. In any norcaradiene tautomer, key atoms C-1 and C-6 have experienced extensive formal rehybridization, the internal bond is probably as sigmoid as cyclopropyl character allows, and the relative geometry of the carbon frame has undergone substantial alteration. This does not mean that norcaradienes cannot display ring current effects in their own right. Compound *(39)*[46–57], for example, exhibits widely divergent cyclopropyl hydrogen shifts and vinyl protons approximately 0.45 ppm downfield from their expected position[58]. Because steric effects and anisotropic contributions from the conjugated diene unit seemingly cannot account for an overall Δδ of this magnitude[58], this evidence has been construed as indicative of homobenzenoid character. However, no structural data is available. In the tricarbonyliron complex *(40)*[59] (C-1—C-6 = 1.52 Å) where the diene segment



(39) (Δδ = 1.66) *(40)* (Δδ = 0.2) *(41)* (Δδ = 1.6)

is now entirely localized, the cyclopropyl protons differ minimally in their shifts. An electronic structure comparable to the uncomplexed system *(39)* is regained upon η^6 bonding as in the chromium complex *(41)*[59] (C-1—C-6 = 1.65 Å)[60]. Given the weight of this evidence and the shortcomings of nomenclature, it would seem most appropriate to distinguish between *(33)*, *(39)*, and their homologs in terms of π- and σ-homoaromatic systems, respectively.

The extent to which the electronic nature of 1,6-methano[10]annulene *(30)* is modified by π-homoaromatic interaction superimposed upon the dominant peripheral 10π electron delocalization remains unclear. The existence of non-negligible 1,6 overlap as suggested by theory[9,61] is seemingly manifested in its photoelectron[62], ultraviolet[63], and ^{13}C-NMR spectra[64]. X-ray crystal structure data for several of its derivatives are available, but like the cycloheptatrienes the C-1—C-6 distances vary widely (1.780—2.257 Å)[65–67] with simple substitution; in fact, the 11,11-dimethyl derivative is a tricyclic bisnorcaradiene[65].

4. Bishomoaromatic Systems

4.1. Cations

The magnitude of homoaromatic stabilization is certain to diminish with increasing interruption by methylene groups of the otherwise conjugated π framework. Under these circumstances, neutral molecules cannot be expected to exhibit homoaromatic character to the same extent as ionic species which continue to possess a reasonable driving force for charge delocalization. A case in point is the 7-norbornenyl cation *(42)*[68], now recognized on the basis of cumulative rate effect



(42)

studies[69], direct NMR spectral examination[70], and responsiveness to varied electron demand[71,72] to be a symmetrical π-bishomocyclopropenium cation and not a rapidly equilibrating pair of classical ions[76]. As expected, the extent of delocalization is critically dependent upon structural geometry. Thus, 4-bromocyclopentene shows no anchimeric assistance to ionization[77], while the annulated homologs *(43)* undergo solvolyses at rates in direct proportion to the level of puckering of the one-carbon bridge (Table 1).

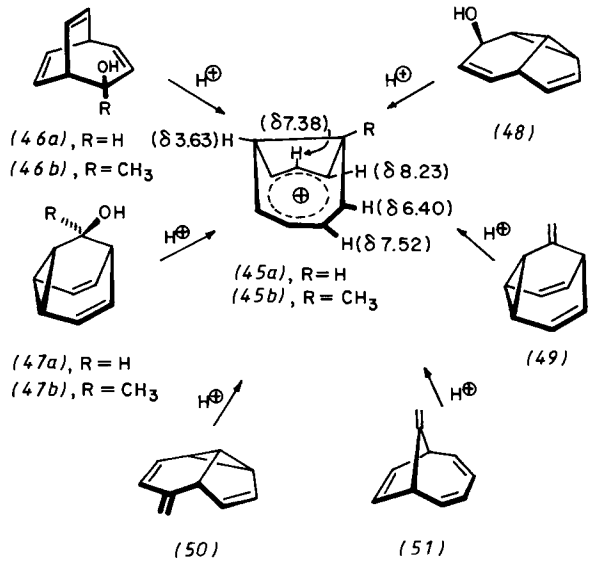


(43) *(44)*

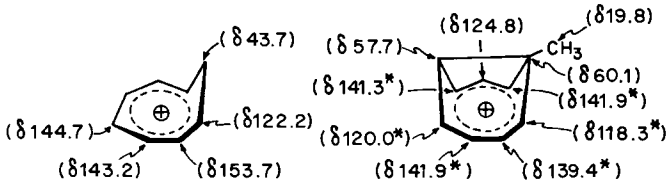
Table 1. Solvolysis constants (k_{rel}) of compounds of type *(43)* and *(44)*, X = OTs.

	n	k_{rel} *(43)*	k_{rel} *(44)*	Ref.
a	1	$10^{14.7}$	10^5	[73]
b	2	10^{11}	1	[2]
c	3	$10^{8.3}$	10^3	[74]
d	4	$10^{4.5}$	$10^{3.5}$	[75]

At the present time, no unbridged 1,4-bishomotropylium cation is known. The bridged system *(45a)* has, however, been generated in superacidic media from a variety of alcohol precursors such as *(46a)*, *(47a)*, and *(48)*[78–80]. Its monomethyl derivative *(45b)* has been comparably prepared from *(46b)* and *(47b)*[80], as well as by protonation of *(49)*—*(51)*[81].

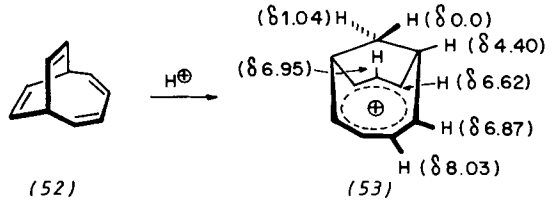


Higher derivatives of *(45)* have been implicated in other electrophilic additions to these methylene hydrocarbons[82]. Evidence for the homoaromatic character of *(45a)* (which is unstable and decomposes above −90°C) and *(45b)* has been deduced largely from spectral observations made under long life conditions. When comparison is made between the ^{13}C-NMR spectra of the monohomotropylium cation and the cation *(45b)*, it is readily seen that, although extensive

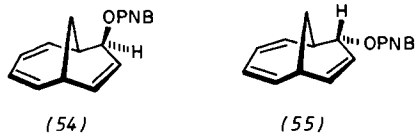


charge delocalization is present in the latter, the level of charge dispersal is reduced relative to the former which exhibits more equitable deshielding of its seven basal carbon atoms. In striking contrast, solvolytic studies provide no apparent indication of rate enhancement consistent with the intermediacy of *(45)*, although 1,4-bishomotropylium ion intervention after the rate-determining step cannot be ruled out[79,80,83].

A second bridged 1,4-bishomotropylium cation *(53)*, so constructed that two methylene hydrogens reside over the

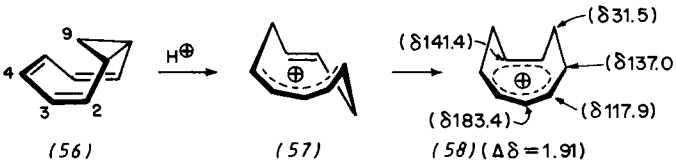


face of the homoaromatic ring system, can be conveniently prepared by dissolution of bicyclo[4.2.2]deca-2,4,7,9-tetraene *(52)* in a superacid medium below −100°C[80,84,85]. The assigned structure with its implied ring current is entirely consistent with the observed coupling constants and the sizable shielding effects (*ca.* 1 ppm) operating on the methylene protons. Other electrophilic additions to *(52)* and its derivatives agree with the mechanistic premise that attack occurs at C-2 with participation by a pair of electrons from one of the ethylene bridges[86–88]. Ion *(53)* appears to have a stronger ring current and to be more delocalized than *(45)*. Also, the substantial *(54)*/*(55)* rate ratio ($10^{4.5}$) signals that anchimeric acceleration can operate in precursors to *(53)*[80].



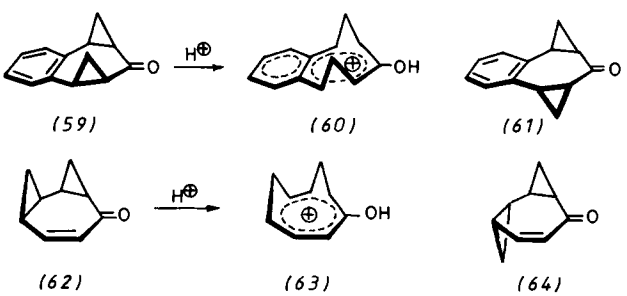
Attempts to generate yet other bridged 1,4-bishomotropylium ions from various precursors have provided some quite unexpected and interesting results[89,90].

Comparable protonation of *cis*-bicyclo[6.1.0]nonatriene is recognized to occur at C-3 in its thermodynamically less stable folded conformation *(56)* with initial generation of transoid cation *(57)* (not observable), the latter experiencing rapid bridge flipping to give the unbridged 1,3-bishomotropylium cation *(58)*[18,91]. The ring current effect in *(58)* is again clearly weaker than in the monohomotropylium derivative.



The requirement that electrophilic attack occur stereoselectively from the *exo* side of *(56)* was tested by examining the reactivity of the *syn*- and the *anti*-9-methyl derivatives. The former cannot attain a folded conformation for obvious steric reasons and in fact proved unreactive under conditions where the *anti* isomer was rapidly transformed into its bishomotropylium counterpart.

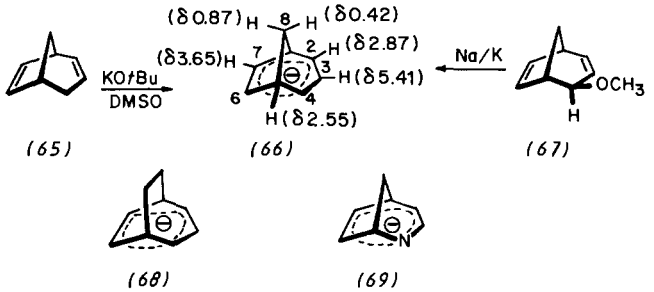
Upon protonation of *(49)*—*(52)* and *(56)*, there is seen to occur electronic and conformational realignments adequate to achieve effective π-bishomoaromatic delocalization. Preformed cyclopropane systems, however, frequently do not possess a comparable capability for structural readjustment. Assessment of the stereochemical requirements for σ-bishomoaromaticity is thereby made possible. In the two pairs of isomers studied so far[92,93], it has been found that *cisoid* bishomotropones *(59)* and *(62)* have internal cyclopropane orbitals properly aligned to enable the attainment of bishomoaromatic character in their conjugate acids *(60)* and *(63)*, respectively. In contrast, *trans* fused arrangements of the bridging groups as in *(61)* and *(64)* are not conducive to such



cyclic delocalization [compare *(57)*] if the chemical shifts of their methylene protons in acidic solution are again suitably diagnostic of the presence of a ring current.

4.2. Anions

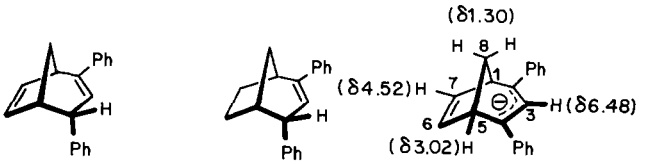
Our present appreciation of 1,3-bishomocyclopentadienide character rests upon several experimental findings. These include the exceptional facility with which bicyclo[3.2.1]octa-2,6-diene *(65)* undergoes proton-deuterium exchange at C-4 to give *(66)*[94], a property shared by its 6,7-benzolog[95] and related molecules[96], and the ^{1}H-NMR spectrum of *(66)*, the direct observation of which was made possible by Na—K reduction of *(67)* (the *endo* isomer reacts much more slowly)[94,97]. Carbanion *(68)*[98] and the hetero system *(69)*[99] exhibit entirely comparable spectral properties suggestive of a sustained ring current. In *(66)*, for example, the upfield chemical shift of H-6 and H-7 and the downfield shift of H-3 compared to those in *(65)* has been construed as indicative of the delocalization of the negative charge over C-6 and C-7. Although the topologies of *(66)*, *(68)*, and *(69)* as enforced by the rather rigid framework geometries are conducive to orbital interaction, and HMO calculations do indicate that this interaction will be bonding[2], a number of findings are not in necessary agreement with the above view. Firstly, one sees that all of the proton shifts in *(66)* appear at high field for a homoaromatic system, thereby indicating that the prevailing diamagnetic ring current, if any, must be small. Secondly, the measurements of deprotonation rates provide information on kinetic properties and need not reflect thermodynamic differences; therefore, the extent to which the anticipated inductive and strain contributions of the second (C-6=C-7) double bond in *(65)* might facilitate carbanion formation is difficult to quantify in absolute terms[100].



(65) *(66)* *(67)*

(68) *(69)*

In this connection, *Trimitsis* and *Tuncay* have recently compared the rate of base-catalyzed hydrogen-deuterium exchange at C-4 in diene *(70)* with that of its dihydro derivative *(71)*[101]. The kinetic imbalance was observed to be only 3.3 (compare $k(65)/k$(dihydro-*(65)*)$=10^{4.5}$)[94] and both rate constants were closely related to that of the acyclic analog 1,3-diphenylpropene where no bishomoaromatic delocalization can develop. Accordingly, it may be argued that the added stabilization provided by the phenyl groups to the developing allylic carbanion moiety eliminates the need for involvement of the 6,7-double bond in charge delocalization. However, the ^{1}H-NMR spectrum of *(72)* bears strikingly close similarity to that of *(66)*[102]. For example, H-6 and H-7 have experienced a substantial upfield shift (1.04 ppm) relative to *(70)* (this is 45% as large as that observed in *(66)*). The bridge protons at C-8 likewise appear upfield [60% as large as that in *(66)*] while H-3 has moved downfield by 1.10 ppm. If *(72)* truly does not display charge delocalization to C-6 and C-7, then it must be concluded that anisotropic effects due to the allyl anion play a more important role in influencing proton shifts than heretofore realized. At best,



(70) *(71)* *(72)*

we see that quantitative dissection of the properties of these anions into σ and π contributions remains incompletely resolved. The desirability of obtaining reliable X-ray structural data wherever this may be possible is again very apparent.

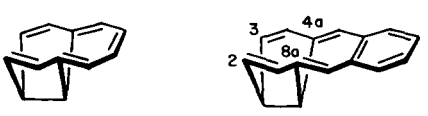
A single attempt to generate a bishomocyclooctatetraenyl dianion has been reported. Reduction to tetraene *(73)* did not however give rise to *(74)* but to a highly basic species where the charge was localized in the triene segment of the molecule[103].



(73) *(74)*

4.3. Neutral Systems

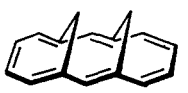
The transition state for degenerate Cope rearrangement in bridged homotropilidenes is bishomobenzenoid in character. The energy gap separating ground state and activated complex is smallest for semibullvalene ($\Delta H^{\neq}=4.8$ kcal/mol)[104]. Prompted by the theoretical conclusions of *Hoffmann*[105] and *Dewar*[106], considerable attention has been paid to the possible creation of a transition state so stabilized that it becomes a neutral homoaromatic ground state. The placement of substituents upon[107], and bracketing of[51,108], the semibullvalene nucleus have so far not led to observation of the desired phenomenon. Extrapolations based upon a recent crystal structure analysis of several 1,5-disubstituted 9-thiabarbaralane 9,9-dioxides[109] suggest that 1,5-difluorosemibullvalene might exhibit this most intriguing property. But the preparation of this fluorocarbon remains to be realized.



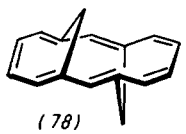
(75) *(76)*

Both *Paquette*[51,110] and *Vogel*[111] have prepared hydrocarbon *(75)* (called elassovalene[110]) and examined its ability to support homoconjugation. The combined weight of spectral evidence[51,110-112] and diamagnetic exaltation criteria[110]

reveal this molecule to possess at a minimum some degree of homoaromatic character in the bridged cycloheptatriene portion of the structure. A more definite assessment of π-electron distribution and structural dimension in this ring system has been realized by synthesis of the 6,7-benzo derivative *(76)* and X-ray structure analysis of this crystalline substance[39]. With precise knowledge of key distances C-4a—C-8a = 2.44 and C-2—C-3 = 2.54 Å and the relative orientations of the p orbitals at these four sites, the respective overlap integrals were determined to be 0.061 and 0.050, respectively. The difference between these values is revealingly sizable and quantitatively indicative of better overlap in the central portion of the molecule. Interestingly, the overlap integral between C-2 and C-3 (see Section 3.3, $S = 0.042$) is somewhat larger than that determined for cycloheptatetriene. It follows from these findings that mutually canted homoconjugated carbon atoms can still interact when separated by internuclear distances as large as 2.54 Å.



(77)



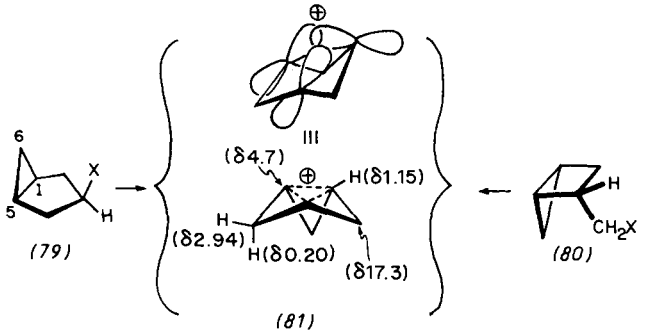
(78)

Although *Vogel* has demonstrated that geometric factors exert important consequences on the electronic properties of higher bridged annulenes such as *(77)* (aromatic)[113] and *(78)* (nonaromatic)[114], it remains unclear in these examples (as in 1,6-methano[10]annulene) if any transannular interaction is at play.

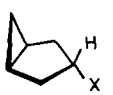
5. Trishomoaromatic Systems

5.1. Cations

On the basis of the solvolytic behavior of *cis* tosylates *(79)*-OTs[115] and *(80)*-OTs[116] which are converted to *(79)*-OAc and *(79)*-OH, respectively, in greater than 90% yield, it has been argued that trishomocyclopropenium cation *(81)* intervenes. This conclusion is supported by the formation from [6,6-D_2]-*(79)*-OTs of *(79)*-OAc having 1.35 methylene protons per cyclopropane ring[117], the direct NMR spectroscopic observation of *(81)* upon ionization of *(79)*-Cl superacid solution at −120 °C[118], and theoretical calculations[119,120]. The spectral data in particular agree with the conclusion that *(81)* is extensively charge-delocalized, possesses C_{3v} symmetry, and gains substantial energetic benefit from homoconjugation.



Despite such evidence, a number of notable failures to generate *(81)* have been reported[121–124]. These include the deamination of *(79)*-NH_2 and *(82)*-NH_2[121] and the solvolysis of *(82)*-OTs[117] which lead to complex product distributions rationalizable in terms of classical cation *(83)*. This led *Winstein* to postulate that leakage from *(83)* to *(81)* is relatively inefficient[117]. In addition, the protonation of bicyclo[3.1.0]hex-2-ene furnishes *(84)* rather than *(81)*[122].



(82)



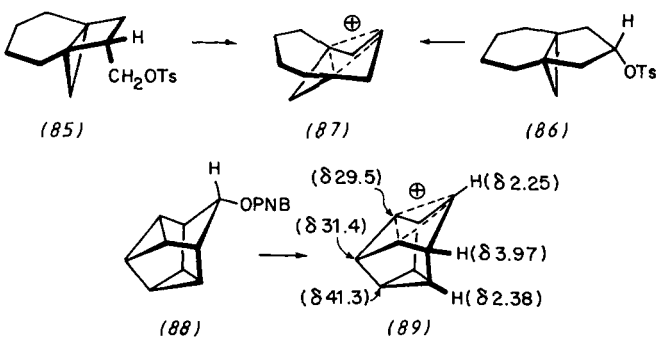
(83)

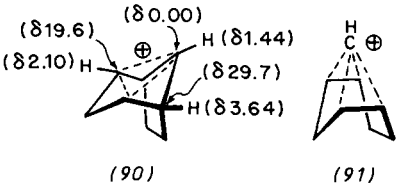


(84)

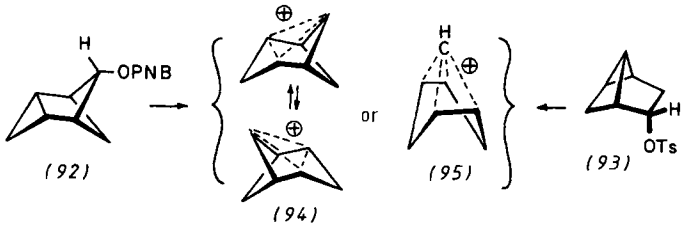
This particular reaction course is now recognized to be thermodynamically justified since the cyclopropylmethyl cation *(83)* is apparently more stable than *(81)*[120].

In recent years, interest in trishomocyclopropenium cations and their precursors has greatly intensified[125–136]. Thus, in addition to the closely related systems *(85)*[125] and *(86)*[58], detailed attention has been paid to *Coates'* cation *(89)*, the highly delocalized nature of which has been uncovered by kinetic studies on *(88)* (rate enhancement of 10^{10} to 10^{12}; strain relief not an issue since rearrangement is degenerate)[126], analysis of remote and proximate substituent effects upon ionization[127], application of the tool of increasing electron demand[128], direct detection by NMR spectroscopy[129], and theoretical analysis[130]. *Masamune* has generated the simpler ethano-bridged cation *(90)* under long-life conditions and has suggested on the basis of the spectral evidence that the square pyramidal species *(91)* may contribute significantly[131]. Whatever the true structure, this trishomoaromatic system does respond to leveling effects[132]. Solvolysis of *(92)*[133] and *(93)*[134] gives a common cation, direct NMR observation of which at −110 °C reveals it to be rapidly equilibrating under these conditions [*i.e. (94)*] or fully delocalized as in *(95)*[135].





Previously, two-fold interruptions of 6π7C tropylium topology were shown not to seriously disrupt charge delocalization



(92) (94) (95) (93)

as long as the methylene carbons were maintained in a *syn* disposition. Simple extrapolation of this reasoning would argue that the tricyclo[5.3.1.$0^{4,11}$]undeca-2,5,8-trienyl cation might well exhibit trishomoaromatic character as depicted in *(96)*. However, neither the solvolysis of *(97)*-OPNB (short-lived conditions)[137] nor exposure of *(97)*-OH, *(97)*-Cl, or

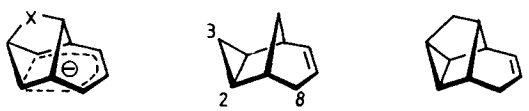


(96) (97)

(97)-OCH_3 to superacidic conditions[137,138] has provided evidence for extended charge delocalization beyond simple allylic character.

5.2. Anions

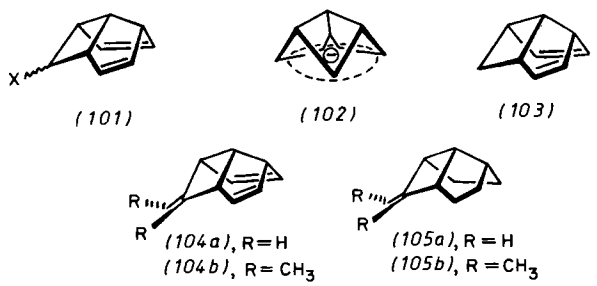
Evidence for extended electronic interaction between an allyl anion and a proximate cyclopropane ring or olefinic bond in potential trishomocyclopentadienide anions has also been sought, but without success. Thus, in *Freeman* and *Hardy*'s attempts to introduce delocalization such as *(98)*



(98) (99) (100)

by deprotonation of *(99)* and *(100)*, no enhancement in the rates of H/D exchange was observed for either hydrocarbon in KO*t*Bu/[D_6]-DMSO[139]. Experiments involving Na/K cleavage of the *exo*-8-methoxy derivative of *(99)* also proved unrewarding[140].

Various reactions of *(101)*-I and *(101)*-Cl (both epimers) have provided no evidence for trishomoaromatic stabilization of the related anion as in *(102)*[141]. Nortriquinacene *(103)* does not experience ready deprotonation at its methylene carbon and in fact MINDO/3 calculations predict this carbanion not only to be classical in structure, but to have a pyramidal anionic carbon as well[141,142]. Furthermore,



(101) (102) (103)

(104a), R=H
(104b), R=CH_3
(105a), R=H
(105b), R=CH_3

photoelectron spectroscopic studies involving *(103)*, *(104)*, and *(105)* indicate the absence of through-space interactions in the alkylidenenortriquinacenes[143].

The presence of a driving force for trishomoaromatic charge delocalization has also not been found in the trishomocyclooctatetraenide dianion *(106)*[103]. Experimentally, reduction of *(107)* gives a highly basic dianion (not observed spectroscopically) which, on the basis of its ensuing reactions, is believed to have the charge concentrated on its diene segment [compare *(27)* and *(74)*][103].



(106) (107)

5.3. Neutral Systems

Three possible uncharged six-electron trishomoaromatic analogs of benzene have been synthesized. They are 1,4,7-cyclononatriene *(108)*[144], triquinacene *(109)*[145], and diademane *(110)*[146]. In the case of *(108)*, it has been concluded from ^{1}H-NMR spectroscopy, heats of hydrogenation studies,



(108) (109) (110)

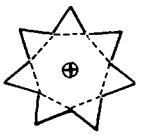
X-ray crystallographic data[147], and theoretical assessments[148] that the triene is not homoaromatic. More recently, however, photoelectron spectroscopy has revealed an appreciable interaction of its π bonds, the 0.9 eV split between the degenerate HOMO's indicating a resonance integral of 0.3 eV[149]. Also, from the distance separating the sp^2-hybridized carbons (distance between bridged π centers 2.46 Å)[147] and the mutual orientation of their inner p lobes, the extent of interaction as measured by the overlap integral is seen to be significant ($S=0.066$)[39]. In *(109)*, the lessened split (0.35—0.4 eV)[150] reveals the lower limit of the resonance integral between its π orbitals (distance = 2.553 Å)[151] to be 0.1 eV. This value is lowered somewhat from its true level because hyperconjugative interactions seemingly destabilize the lowest π orbital, causing the split to be smaller than it would if through-space interactions operated exclusively. Notwithstanding, the homoconjugation in *(109)*, as enforced by its unique topology, is measurably decreased ($S=0.054$)[39] relative to *(108)*. Diademane *(110)* lacks even this level of interaction[152].

6. Higher Homoaromatic Systems

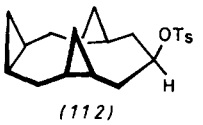
Winstein has attempted to gain access to the perhomotropylium cation *(111)* through solvolysis of *(112)* and its epimer[153]. But the homoaromatic species is not formed, the rates, products, and lack of deuterium scrambling suggesting that delocalized intermediates are unimportant.

Triscyclopropanation of *(108)* in all *cis* fashion leads to adoption by the resultant saturated hydrocarbon of a crown

conformation which so fixes the medium ring methylene groups that the inner protons experience strong shielding while the outer protons are deshielded[154]. Yet when the

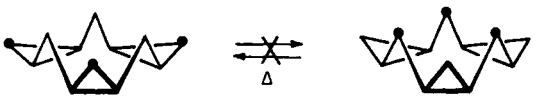


(111)



(112)

two hexadeuterio isomers *(113)* and *(114)* were recently prepared and thermolyzed, no scrambling of the isotopic label was seen[155]. The lack of bond shifting, as well as the demonstrated noninterconvertibility of two trioxa analogs[156], signals the unresponsiveness of this class of compounds to the attainment of "hexahomobenzenoid" transition states.



(113) (114)

7. Summary

In light of the above findings, we see that proper structural modification of a variety of molecular systems possessing $(4n+2)$ π electrons or a suitable array of π and strained σ (cyclopropane) electrons can indeed remain conducive to maintenance of a ring current. But through-space interaction between the composite segments is acutely sensitive to geometry, mutual proximity, and energy levels of the relevant orbitals. Such effects are not unique to homoaromatic molecules. For bridged bicyclic dienes of the Dewar benzene, norbornadiene, bicyclo[2.2.2]octadiene, *etc.*, type, the same is true. In this series, through-space interaction becomes greatly attenuated with incremental lengthening of the oligomethylene bridge (from 0 to 4 carbon atoms)[157].

As the number of insulating atoms is increased, the ability to satisfy these major requirements becomes more and more taxed. This is particularly noticeable for neutral molecules which lack the driving force for charge dispersal embodied in ions. For such substances, crystal structure data are necessary to give quantitative meaning to the extent of orbital overlap. This refined treatment is, of course, equally valuable for ions, but the experimental task in these cases is understandably more complicated.

Although the future will undoubtedly bring refinements and expanded dimension to this field of study, a certain number of concepts dealing with novel forms of conjugation extended over three dimensional space have already gained attention in recent years. And beyond bicycloaromaticity[5], ribbon topology[142], spiroconjugation[158], and subjacent orbital control[159] lie new frontiers of understanding which will continue to challenge practicing chemists.

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COMMUNICATIONS

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Asymmetric Synthesis of α-Alkyl-α-aminocarboxylic Acids by Alkylation of 1-*chiral*-Substituted 2-Imidazolin-5-ones[1]

By *Ulrich Schöllkopf, Hans Heinrich Hausberg, Inga Hoppe, Marcos Segal*, and *Udo Reiter*[*]

Owing to the immensely important role played by optically active amino acids in pure and applied chemistry, asymmetric amino acid synthesis has attracted especial interest. Of preparative importance, however, are only those methods which a) are relatively easy to carry out with good chemical yields, b) give high optical yields, and c) enable recovery of the chiral auxiliary agent[2].

We wish to report an asymmetric synthesis of α-alkyl-α-amino acids *(11)*, which in many cases satisfies these requirements[3]. The 4-metalated 4-alkyl-1-[(*S*)-1-phenylethyl]-2-imidazolin-5-ones *(7b)* or their tautomers *(8)* are alkylated with R^2-Hal *(9)* and the resulting 4,4-disubstituted imidazolinones *(10)* hydrolyzed to the amino acids *(11)*. After the hydrolysis the (*S*)-1-phenylethylamine *(2)* used for the synthesis of *(7)*, can be recovered. In the case of alkylating agents *(9)* with large R^2 groups, *e.g.* benzyl halides, the asymmetric induction at C-4 of *(10)* is almost 100%; it decreases with decreasing size of R^2 (cf. Table 1). The stereoselectivity of the reaction can be determined ^{1}H-NMR spectroscopically at the stage of the imidazolinone *(10)* (usually at 60 MHz and without shift reagents), preferably by observing the doublet of the methyl protons of the phenylethyl moiety, which shows different chemical shifts in the two diastereomers. An induction of >95% (cf. Table 1) is assumed if only one diastereomer is recognizable in the NMR spectrum.

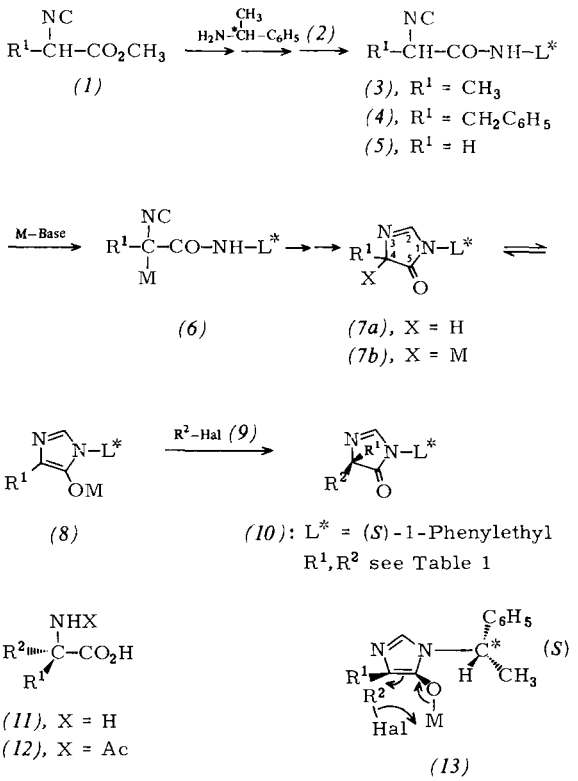
The 2-imidazolin-5-ones *(7a)* are obtained either from the (*S*)-α-amino *N*-phenylethylcarboxamides with orthoformates[4] or, better, by base-induced cyclization of the (*S*)-*N*-phenylethyl-2-isocyanoalkanamides *(3)*—*(4)*. Isolation of the imidazolinone *(7a)* is, however, unnecessary. Reaction of the amides *(3)* to *(4)*—prepared from methyl 2-isocyanoalkanoate *(1)* and (*S*)-1-phenylethylamine *(2)*—with one equivalent of a metalating agent (M-base such as butyllithium, potassium *tert*-butoxide, sodium hydroxide *etc.*) leads to the 4-metalated imidazolinones *(7b) in situ*. The cyclization *(6)* →→ *(7b)* proceeds apparently rapidly, so that the same results can be achieved with this (more convenient) *in situ* method [Method A, cf. Table 1] as when starting from *(7a)*. In some experiments we used (*S*)-*N*-phenylethylisocyanoacetamide *(5)* as starting compound. Twofold metalation

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of *(5)* with two equivalents of butyllithium and subsequent reaction with R^1-Hal afforded the intermediate *(6)*, M = Li, which cyclized to *(7b)*⇌*(8)*, from which *(10)* was finally obtained by reaction with R^2-Hal [Method B, cf. Table 1]. In order to achieve the highest possible optical yield *via* this route it would seem advisable to first incorporate the smaller substituents as R^1-Hal [cf. in Table 1 *e.g. (10a)* with *(10o)*, *(10j)* with *(10p)*]. As expected the preferred configuration at C-4 of *(10)* changes if the sequence of incorporation of R^1 and R^2 is changed [cf. in Table 1 *e.g. (10a)* with *(10o)*, *(10n)* with *(10t)*, *(10l)* with *(10q)*].

Hydrolysis of the 4,4-disubstituted imidazolinones *(10)* necessitates more or less drastic conditions, depending on the nature of R^1 and R^2. In principle, the hydrolysis can be carried out under acid or alkaline conditions. Thus, *e.g.*, we obtained (*S*)-α-methylphenylalanine *(11a)* by acid hydrolysis [from *(10a)*][5], but later found out that alkaline hydrolysis (with KOH in ethanol/water, glycol/water *etc.*) was more suitable[6]. The amino acids *(11)* have been characterized by way of their (readily crystallizing) *N*-acetyl derivatives *(12)*[6].

With (*S*)-configuration of the 1-phenylethyl group (L*)—as revealed by the synthesis of the configuratively known (*S*)-α-methylphenylalanine[3] *(11a)* and (*S*)-α-methyl-DOPA[6]—the configuration shown in formulas *(10)* and *(11)* is induced [*S* when R^2 has priority over R^1, otherwise *R*]. The following model concept explains this finding: in the most favorable conformation for *(8)* the hydrogen atom in the ring plane of the heterocycle is oriented towards the oxygen atom[7], which—complexed with metal atom and solvent—is the "largest" neighbor. Methyl and phenyl groups lie below and above the diastereotopic heterocyclic plane [cf. *(13)*]; for steric reasons R^2 preferably enters at that side which bears the smaller methyl group. Accordingly, the degree of induction depends on the size of the entering group R^2 [cf. in Table 1 *e.g.*



(10o) with *(10n)*], and not on that of the stationary substituents R^1 [cf. in Table 1 *(10a)*, *(10i)*—*(10n)*][8].

Experimental

(*S*)-*N*-phenylethyl-2-isocyanoalkanamides *(3)*—*(5)*: (*S*)-1-phenylethylamine *(2)* (12.1 g, 0.1 mol) and *(1)* (0.1 mol) are

Table 1. Synthesized 2-imidazolin-5-ones *(10)* and *N*-acetylamino acids *(12)*.

				(10)			*(12)*	
	R^1	R^2	Method [a]	Yield [b] [%]	Optical yield [b]	Config.	$[\alpha]_D^{21}$ (c, Solvent) [c]	M.p. [°C]
(a)	CH_3	$CH_2C_6H_5$	A	60	>95, 90 [d]	*S*	− 4.7° (1.05, 1 N HCl) [e]	
			B	86	100	*S*		
(b)	CH_3	CH_2—C_6H_3-3,4(OCH_3)$_2$	[f]	90	66	*S*	−28.8° (2.0, CH_3OH) [g]	
(c)	CH_3	CH_2—C_6H_4-4(OCH_3)	A [d]		72 [5]	*S*	− 4.4° (1.0, 1 N HCl) [h] [5]	
(d)	CH_3	(1-Naphthyl)methyl	A	84	>95	*S*	−91.38° (1.08, CH_3OH)	222
(e)	CH_3	(2-Naphthyl)methyl	A	87	>95	*S*	−92.31° (1.62, CH_3OH)	212
(f)	CH_3	(2-Thienyl)methyl	A	80	>95	*S*	−37.5° (1.0, CH_3OH)	224
(g)	CH_3	(3-Benzothienyl)methyl	A	87	>95	*S*	−69.5° (1.0, DMF)	244
(h)	CH_3	(2-Bromo-3-benzofuranyl)methyl	A	88	>95	*S*	−77.6° (1.0, CH_3OH)	239
(i)	C_2H_5	$CH_2C_6H_5$	B	85	95	*S*	−19.01° (1.875, CH_3OH)	223–225
(j)	$CH_2CH{=}CH_2$	$CH_2C_6H_5$	B	75	90	*S*	−21.8° (1.665, CH_3OH)	264–265
(k)	*n*-C_3H_7	$CH_2C_6H_5$	B	77	90	*S*	−12.9° (1.419, CH_3OH)	238–240
(l)	*i*-C_3H_7 [i]	$CH_2C_6H_5$	B	78	95	*R*		
(m)	C_4H_9 [i]	$CH_2C_6H_5$	B	67	95	*S*	− 8.49° (1.46, CH_3OH)	199–200
(n)	CH_2—C_6H_4—4Br	$CH_2C_6H_5$	B	72	100	*R*		
(o)	$CH_2C_6H_5$	CH_3	A	89	20	*R*		
(p)	$CH_2C_6H_5$	$CH_2CH{=}CH_2$	A	86	43	*R*		
(q)	$CH_2C_6H_5$	*i*-C_3H_7 [i]	A	62	65	*S*		
(r)	$CH_2C_6H_5$	C_4H_9	A	72	55, 50 [d]	*R*		
(s)	$CH_2C_6H_5$	CH_2CO_2Et	A	75	31	*S*		
(t)	$CH_2C_6H_5$	CH_2—C_6H_4—4Br	A	87	100	*S*		

[a] If not otherwise stated, with butyllithium as M-base and bromides as *(9)*.
[b] Determined on crude product.
[c] If not otherwise stated, optically pure.
[d] With potassium *tert*-butoxide.
[e] For *(11a)*. Ref. [3]: −4.5° (1.0, 1 N HCl).
[f] After *Mąkosza*, with veratryl chloride, 50%. NaOH, TEBA, CH_2Cl_2, 25—40°C.
[g] 55% ee; optically pure *(12b)*: −52° (2.0, CH_3OH) [6].
[h] For *(11c)*.
[i] With iodide.

mixed together with 0.1 g *p*-toluenesulfonic acid with stirring. *(3)*: 11.3 g (0.1 mol) *(1a)*, 12 h at room temperature, 30 min at 100 °C; crystallization from methanol or chromatography on alumina with ether; 16.4 g (81 %) *(3)*, m.p. 89 °C. *(4)*: 18.9 g (0.1 mol) *(1b)*, 12 h at 60 °C, then methanol removed *in vacuo*; 26.5 g (95 %) *(4)*, m.p. 135—136 °C (from isopropanol). *(5)*: 9.9 g (0.1 mol) *(1c)*, 12 h at 30—35 °C without catalyst, otherwise as in the case of *(4)*; 15 g (80 %) *(5)*, m.p. 122—123 °C (from ethyl acetate).

2-Imidazolin-5-ones *(7a)*: To a solution of *(3)* or *(4)* in tetrahydrofuran at −60 °C is added 1 equivalent of butyllithium or potassium *tert*-butoxide and the stirred mixture warmed to −20 °C, neutralized with glacial acetic acid, and worked up in the usual way. *(7a)*, $R^1 = CH_3$: b.p. 105 °C/10^{-3} torr (with enol form). *(7a)*, $R^1 = CH_2C_6H_5$: used as crude product (no enol form detectable). *(7a)*, $R^1 = H$: not preparable, unstable.

2-Imidazolin-5-ones *(10)*: Method A: To a solution of *(3)* (3.03 g, 15 mmol) in 20 ml dry tetrahydrofuran at −60 °C is added 15 mmol butyllithium (dropwise) (9.4 ml of a 1.6 M solution in hexane) or 15 mmol potassium *tert*-butoxide. A solution of 15 mmol R^2-Hal *(9)* in *ca.* 10 ml tetrahydrofuran is added dropwise at −60 °C to the solution of *(7b)*⇌*(8)*. The mixture is allowed to warm to room temperature, the solvent removed *in vacuo*, and the residue taken up in 20 ml CH_2Cl_2. The solution is washed with 2 × 20 ml water, dried over magnesium sulfate, and worked up in the usual way (cf. Table 1).—In the case of *(4)*, 0.84 g (3 mmol) in 15 ml THF is metalated with 3 mmol BuLi at −78 °C. For the cyclization *(6)* → *(7)* the solution is allowed to warm to room temperature. It is then cooled to −70 °C and treated with 3 mmol *(9)*. After 3 h at room temperature the solution is neutralized with glacial acetic acid, the solvent removed, and the residue worked up in the usual way.—Method B: 20 mmol butyllithium (13 ml of a 1.5 M solution in hexane) is added dropwise at −78 °C to a solution of *(5)* (1.9 g, 10 mmol) in 25 ml THF. The mixture is stirred for 10 min, treated with a solution of 10 mmol R^1-Hal in 10 ml THF, and then allowed to warm to +10 °C. Finally, 10 mmol *(9)* in 10 ml THF is added and the whole stirred for *ca.* 2 h. Work-up as in Method A.

Amino acids *(11)* and *(12)*: A mixture of 2 g of *(10)*, 20 ml ethanol, 10 ml water and 2 g KOH (if need be, glycol or triglycol instead of ethanol) is boiled under reflux until completion of hydrolysis (up to 20 h). Water is then added, if necessary after removal of the ethanol, and the solution extracted twice with CH_2Cl_2 [separation of *(2)*]. Further work-up depends upon the properties of *(11)*. On acidification of the aqueous phase with 6 N HCl, *(11)* often precipitates. In other cases the aqueous phase is neutralized and evaporated down *in vacuo*. The crude product (contaminated with KCl) can be used for the acylation: A solution of *(11)* (1 g) in dimethylformamide (10 ml) is treated with 2-equivalents of acetic anhydride and the mixture heated for 1 h at 90 °C. The solution is then evaporated down at 10^{-2} torr and *(12)* isolated by recrystallization from ethanol or ethanol/water.

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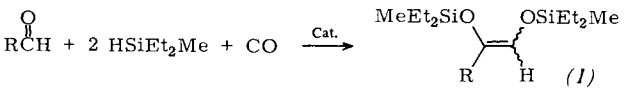
[1] Asymmetric Syntheses *via* Heterocyclic Intermediates, Part 1.
[2] For known methods, some of which, however, do not fulfill all these requirements, cf. *H. B. Kagan, T. P. Dang*, J. Am. Chem. Soc. *94*, 6429 (1972); *W. S. Knowles, M. J. Saback, B. D. Vineyard, D. J. Weinkauff, ibid. 97*, 2567 (1975); *E. J. Corey, R. J. McCaully, H. S. Sachdev, ibid. 92*, 2476 (1970); *B. W. Bycroft, G. L. Lee*, J. Chem. Soc. Chem. Commun. *1975*, 988; *S. Yamada, T. Oguri, T. Shioiri, ibid. 1976*, 136; *U. Schmidt, E. Öhler*, Angew. Chem. *88*, 54 (1976); Angew. Chem. Int. Ed. Engl. *15*, 42 (1976).
[3] For a Strecker synthesis of α-methyl-α-amino acids, which proceeds with high optical yield *via* an asymmetric rearrangement of the second kind, but in which the chiral reagent is destroyed, cf. *K. Weinges, G. Graab, D. Nagel, B. Stemmle*, Chem. Ber. *104*, 3594 (1971); *K. Weinges, K. Gries, B. Stemmle, W. Schrank, ibid. 110*, 2098 (1977).
[4] *W. Böll, H.-J. May*, BASF AG, private communication.
[5] *H.-H. Hausberg*, Dissertation, Universität Göttingen 1976.
[6] *W. Böll*, BASF AG, private communication.
[7] According to an X-ray structure analysis the hydrogen atom of the 1-phenylethyl group in *(10a)* lies in the plane of the heterocycle and points towards the oxygen; moreover, the benzyl group inserted at C-4 is located on the same side as the methyl group of the phenylethyl moiety, its phenyl ring is located near the carbonyl group: *W. Saenger*, Max-Planck-Institut für Experimentelle Medizin, Göttingen, private communication.
[8] If a methyl group is inserted at C-2 in *(7b)*⇌*(8)*, the extent of induction is drastically reduced.

The $Co_2(CO)_8/Ph_3P$-Catalyzed Reaction of Aldehydes with Hydrosilane and Carbon Monoxide[1]

By *Yoshio Seki, Shinji Murai*, and *Noboru Sonoda*[*]

We recently reported that olefins[2] and cyclic ethers[3] give enol silyl ethers and silyl-protected hydroxyaldehydes, respectively, when allowed to react with a hydrosilane and carbon monoxide in the presence of $Co_2(CO)_8$.

We now wish to report the new catalyzed reaction of aldehydes with $HSiR_3$ and CO to give 1,2-bis(siloxy)olefins *(1)*.



(1)

Table 1. Physical properties of some silyl-protected 1,2-enediols *(1)*.

	R	B.p. [°C/torr]	IR [a] ν (C=C) [cm^{-1}]	^{1}H-NMR [b] δ (HC=C, s)
(1a)	*n*-Hexyl	120—123/0.5	1685	5.44 and 5.90
(1b)	*n*-Propyl	130—150/25	1685	5.44 and 5.92
(1c)	Cyclohexyl	140—150/0.8	1685	5.48 and 5.78
(1d)	$Et_2MeSiO(CH_2)_4$	155—165/0.4	1685	5.44 and 5.92

[a] Without solvent.
[b] In CCl_4. The signals at higher fields correspond to (*Z*) isomers and those at lower field to (*E*) isomers.

Reaction of *n*-heptanal with diethyl(methyl)silane (threefold excess w.r.t. aldehyde) and carbon monoxide in the presence of $Co_2(CO)_8$ and triphenylphosphane gave a mixture of (*E*)- and (*Z*)-1,2-bis[diethyl(methyl)siloxy]-1-octenes *(1a)* in 66 % yield (cf. Table 1). The use of Ph_3P as a cocatalyst is necessary

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to prevent undesired hydrosilylation of the aldehyde. Analogously, reaction of *n*-butanal and cyclohexanecarboxaldehyde gave *(1b)* and *(1c)* in 67 % and 37 % yields, respectively. In the case of cyclohexanecarboxaldehyde, the yield of *(1c)* was low because of the formation of diethyl(methyl)siloxymethylenecyclohexane (61 %) by dehydrogenative silylation. Interestingly, a similar reaction (using a fivefold excess of the hydrosilane, but in this case without Ph_3P) of tetrahydrofuran was found to give the same type of compound *(1d)* in 89 % yield—probably *via* the intermediate 5-diethyl(methyl)siloxy-*n*-pentanal, which was the product when the reaction was carried out using a fivefold excess of tetrahydrofuran over the silane and without Ph_3P[3].

It has been reported that formates can be produced from aldehydes (*via* O—C bond formation) under hydroformylation (oxo synthesis) conditions[4]. In contrast, by using a hydrosilane instead of hydrogen, bis-siloxyalkenes *(1)* instead of esters were obtained (*via* C—C bond formation).

Experimental:

Synthesis of *(1a)*: A solution of 1.14 g (10 mmol) of *n*-heptanal, 4.4 ml (30 mmol) of diethyl(methyl)silane, 0.068 g (0.2 mmol) of $Co_2(CO)_8$, and 0.052 g (0.2 mmol) of triphenylphosphane in 20 ml of benzene was placed in a 100 ml stainless steel autoclave. The autoclave was flushed with N_2 (50 kp/cm^2) and CO (50 kp/cm^2), then charged with CO (50 kp/cm^2) and heated at 140 °C with stirring. After 20 h, the autoclave was cooled and depressurized. Analysis of the reaction mixture by GLC [Silicon OV-1, 5 %, on Uniport KS, 3 m, 170 °C, internal standard *n*-hexadecane] showed it to contain *(1a)* in 66 % yield; at longer retention times there were at least two further unidentified products (total *ca.* 14 %). An analytical sample of *(1a)* was obtained by fractional distillation (b.p. 120–123 °C/0.5 torr) and preparative gas chromatography (190 °C).

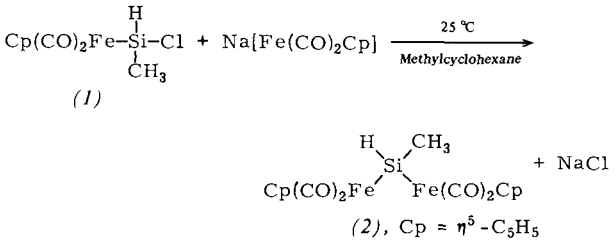
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CAS Registry numbers:
$Co_2(CO)_8$, 10210-68-1; diethyl(methyl)silane, 760-32-7; carbon monoxide, 630-80-0

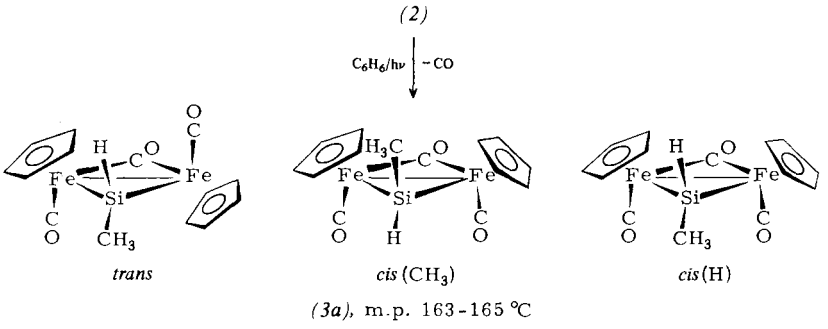
Binuclear Iron Complexes Containing Unsymmetrically Substituted Silanediyl Bridges[1]

By *Wolfgang Malisch* and *Wolfgang Ries*[*]

The ability of 4B elements germanium, tin, and lead to function as bridges between transition metal atoms has been demonstrated by numerous examples[2], whereas only few corresponding examples of complexes with silicon bridges have so far been described[3]. We have now found that nucleophilic metalation of chlorosilyliron complexes of type *(1)*[4] with the extremely reactive anion $[Cp(CO)_2Fe]^{\ominus}$[5] affords easy access to binuclear complexes containing a silicon bridge if the chlorosilyl group still bears at least one hydrogen atom and the reaction is carried out heterogeneously in methylcyclohexane.



Diferriosilane *(2)*, which is isolable as orange-yellow crystals, m.p. 89—90 °C, exhibits increasing solubility in the series pentane cyclohexane, benzene, toluene, and, according to the IR spectrum, has C_1 symmetry[6] in the dissolved state (cyclohexane). The prochiral character of the $Cp(CO)_2Fe$ group is demonstrated by ^{13}C-NMR spectroscopy[1]. The unusual position of the νSiH vibrational band at 2025 cm^{-1} characterizes the metal group as a strong donor. This "transition metal effect" also gives rise to the pronounced tendency of the strongly hydridic *Si*—H function to undergo exchange reactions, as exemplified by the halogenation of the latter on reaction with CCl_4 or $PhC^{\oplus}BF_4^{\ominus}$ under very mild conditions (in benzene, 25 °C)[1].



(3a), m.p. 163–165 °C

When *(2)*, either in the solid state or in solution, is exposed to daylight it is slowly transformed with loss of CO into the bicyclic species *(3a)*, in which the two iron atoms are now coupled both directly and by a CO bridge. This conversion can be considerably accelerated photochemically[7].

The ^{1}H-NMR spectrum of *(3a)* in benzene contains, besides four signals for the cyclopentadienyl groups, three signals each for the HSi and the CH_3 groups (as quartet and doublet, respectively) and thus proves that the ring system is present

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[1] Transition Metal Reactions of Silanes. Part 5.—Part 4: see Ref. [2c].
[2] a) *Y. Seki, A. Hidaka, S. Murai, N. Sonoda*, Angew. Chem. *89*, 196 (1977); Angew. Chem. Int. Ed. Engl. *16*, 174 (1977); b) *Y. Seki, A. Hidaka, S. Makino, S. Murai, N. Sonoda*, J. Organomet. Chem. *140*, 361 (1977); c) *Y. Seki, S. Murai, A. Hidaka, N. Sonoda*, Angew. Chem. *89*, 919 (1977); Angew. Chem. Int. Ed. Engl. *16*, 881 (1977).
[3] *Y. Seki, S. Murai, I. Yamamoto, N. Sonoda*, Angew. Chem. *89*, 818 (1977); Angew. Chem. Int. Ed. Engl. *16*, 789 (1977).
[4] *R. F. Heck*: Organotransition Metal Chemistry, A Mechanistic Approach. Academic Press, New York 1974, p. 218; *F. Piacenti, M. Bianchi in I. Wender, P. Pino*: Organic Syntheses *via* Metal Carbonyls, Vol. 2. Wiley, New York 1977, pp. 12, 37.

in solution as a mixture of all three theoretically conceivable stereoisomers[8]. An unequivocal assignment of signals (cf. Table 1) is possible only in the case of the *trans* form (two C_5H_5 signals of equal intensity). Assuming steric preference for the *cis*(H) form an isomeric ratio of 56/*cis*(H): 26/*cis*(CH_3): 18/*trans* would result. Spectra recorded immediately after dissolution of crystalline *(3a)* show only the two *cis* isomers [86/*cis*(H): 14/*cis*(CH_3)], while the equilibrium concentration of the *trans* form is reached only after 20 minutes. Hence, a *cis*/*trans* isomerization already takes place at room temperature, and, in principle, is possible both from the *cis*(H) as well as from the *cis*(CH_3) form[9].

Table 1. Spectroscopic data of the μ-silanediyliron complexes *(2)*, *(3a)* and *(3b)* [a].

(2): ^{1}H-NMR (C_6H_6): $\delta C_5H_5 = 4.37$ (s, 10H); $\delta CH_3 = 1.14$ (d, 3H), $^3J_{HCSiH} = 3.6$; $\delta HSi = 5.46$ (q, 1H).—^{13}C-NMR (C_6D_6): $\delta C_5H_5 = 84.3$; $\delta CH_3 = 12.0$; $\delta_1 CO = 216.52$; $\delta_2 CO = 216.65$.—^{29}Si-NMR (C_6D_6): $\delta Si = 62.8$.—IR (cyclohexane): νCO = 1990 (vs), 1952 (s), 1943 (s), 1935 (m) cm^{-1}.

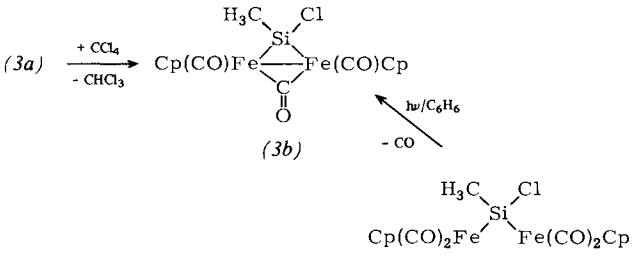
(3a): ^{1}H-NMR (C_6D_6):	δC_5H_5 (s, 5H bzw. 10H)	δCH_3 (d, 3H)	$^3J_{HCSiH}$	δSiH (q, 1H)
trans	$\delta_1 = 4.37$ $\delta_2 = 4.29$	1.38	3.6	7.38
cis(H)	4.16	1.47	3.8	7.77
cis(CH_3)	4.09	1.24	3.7	6.91

IR (cyclohexane): νCO = 1999 (w), 1976 (vs), 1958 (s), 1939 (s), 1794 (sh) cm^{-1}.

(3b): ^{1}H-NMR (C_6D_6): *trans*: $\delta C_5H_5 = 4.42$, 4.28 (s, 5H); $\delta CH_3 = 1.62$ (s, 3H) / *cis*(Cl): $\delta C_5H_5 = 4.23$ (s, 10H); $\delta CH_3 = 1.71$ (s, 3H)) / *cis*(CH_3): $\delta C_5H_5 = 4.03$ (s, 10H); $\delta CH_3 = 1.59$ (s, 3H).—IR (cyclohexane): νCO = 2000 (w), 1980 (vs), 1968 (sh), 1946 (s), 1791 (vs) cm^{-1}.

[a] Chemical shifts downfield rel. to TMS int.; coupling constants in Hz. Analytical data consistent with the given formulas.

In accord with the even smaller magnitude of the Si—H valence vibration (νSiH = 2015 cm^{-1}), hydrogen exchange at the silanediyl bridge of *(3a)* proceeds more rapidly than in the open-chain species *(2)*.



Reaction of *(3a)* with CCl_4 smoothly affords the chloro-substituted cyclic compound *(3b)*, m.p. 183—185 °C, which is distinctly more stable than the hydrosilane *(3a)* (both thermally and solvolytically), and in which the isomeric equilibrium is shifted further in favor of the *cis*(X) form [83/*cis*(Cl): 5/*cis*(CH_3): 12/*trans*]. The derivative *(3b)* can also be generated photolytically from *(4)*[11].

Experimental:

(2): A solution of $Cp(CO)_3FeSiHCH_3Cl$[4] (1.57 g, 6.12 mmol) in 50 ml methylcyclohexane is treated with 1.58 g (7.88 mmol) of dry $Na[Fe(CO)_2Cp]$[5]. The mixture is stirred in the absence of light for 6d at 25 °C, filtered, the filtrate evaporated *in vacuo*, and the resulting residue extracted several times with pentane. Freezing out at −78 °C affords 1.43 g (59 %) *(2)*.

(3a): A solution of *(2)* (492 mg, 1.24 mmol) in 60 ml benzene is irradiated for *ca.* 6 h with UV light (quartz lamp Q150 Hanau), the carbon monoxide that is formed being removed from the reaction vessel with a stream of N_2. The filtered solution is concentrated to 7 ml and *(3a)* precipitated with 5 ml pentane at room temperature. The deep-red crystals are washed twice with 5 ml cold pentane and dried *in vacuo*; yield 271 mg (59 %).

(3b): A suspension of *(3a)* (270 mg, 0.73 mmol) in 5 ml CCl_4 is allowed to stand for 30 min at 25 °C. After removal of volatile components, multiple extraction of the solid residue with 10 ml toluene/methylcyclohexane (1 : 1) and freezing out at −78 °C affords 242 mg (82 %) *(3b)*.

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[1] Synthesis and Reactivity of Silicon-Transition Metal Complexes, Part 13. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 12: *W. Malisch, W. Ries*, Chem. Ber., in press.
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[6] The intensities of the νCO bands (Table 1) decrease monotonically with decreasing wave number. Cf. *N. Flitcroft, D. A. Harbourne, I. Paul, P. M. Tucker, F. G. A. Stone*, J. Chem. Soc. *A 1966*, 1130.
[7] An analogous cyclization reaction has already been observed with $(CH_3)_2Ge$-bridged complexes: *R. C. Job, M. D. Curtis*, Inorg. Chem. *12*, 2514 (1973).
[8] This finding is confirmed by the $^{13}C\{^1H\}$-NMR spectrum (in C_6D_6). $\delta C_5H_5 = 83.83$, 84.27, 84.86, 85.30; $\delta CH_3 = 7.89$, 8.97, 10.09; $\delta CO_{term} = 212.57$.
[9] Investigations presently being carried out on the activation parameters of this process should clarify whether the *cis*/*cis* and *cis*/*trans* isomerizations are independent processes.

Oxepinobenzofurans—The True Nature of Sterically Hindered "Benzoxetes"

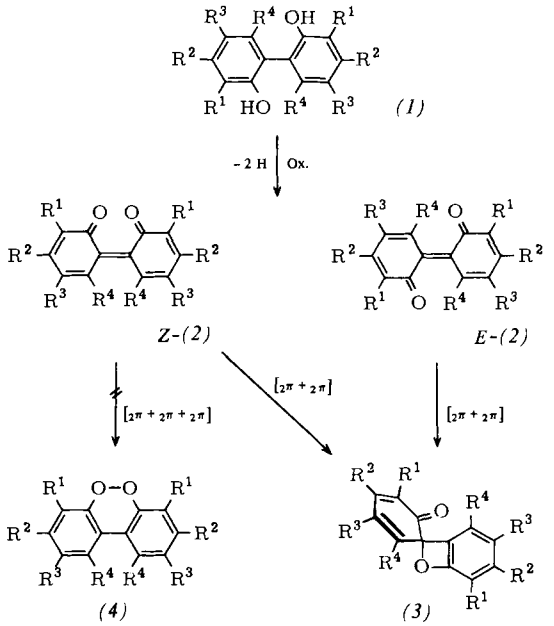
By *Herbert Meier, Hans-Peter Schneider, Anton Rieker*, and *Peter B. Hitchcock*[*]

In 1961 *E. Müller et al.* observed that dehydrogenation of 2,4-di-*tert*-butylphenol, 2,4-di-*tert*-butyl-6-iodophenol, or biphenol *(1a)* in benzene yields a deep violet solution suspected to contain the corresponding *o,o'*-diphenoquinone *(2a)* (*Z*- and/or *E*-configuration). A pale yellow compound, assigned the structure of a benzoxete *(3a)*, could be isolated in good yield[1].

Structural proof was based on the formal analogy to the formation of homologous spiroquinol ethers, reduction to the biphenol *(1a)*, and the ^{1}H-NMR spectrum[1]. Later on, compound *(4a)* first isolated by *Baltes* and *Volbert* in 1955, which exists in equilibrium with the diphenoquinone *(2b)*[2a], was ascribed the same kind of structure *(3b)*[2b,c]. The oxidation products of the biphenols *(1c—g)* were also regarded

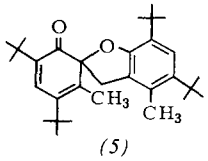
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as benzoxetes *(3c—g)*[3]. Further synthetic pathways leading to these "benzoxetes" and numerous reactions have been reported up to the present[4].



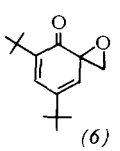
	R^1	R^2	R^3	R^4
(a)	*t*Bu	H	*t*Bu	H
(b)	*t*Bu	H	OMe	H
(c)	*t*Pent	H	*t*Pent	H
(d)	*t*Bu	H	Trityl	H
(e)	*t*Bu	H	*t*Bu	Me
(f)	*t*Bu	H	*t*Bu	Cl
(g)	*t*Bu	Cl	OMe	Cl

According to an EHT calculation[5], valence isomerization of *o*-methylenecyclohexadienone to benzoxete should be a strongly endothermic process. This is incompatible with the low activation barrier of isomerization of compound *(2)*, which proceeds spontaneously at room temperature. Moreover, the thermal and chemical behavior of the products contradict observations made on benzoxete systems formed *in situ*[6]. We have therefore re-examined the valence isomers of the diphenoquinones *(2a)*, *(2b)*, *(2f)*, and *(2g)* and found that the IR absorption observed in the region of 1645 cm^{-1} cannot be assigned to the C=O stretching absorption of a *o*-quinol ether on account of its wave number and intensity. In the ^{13}C-NMR spectra the presence of a carbonyl carbon atom of a quinol ether structure can likewise be strictly ruled out. Compounds *(5)*[1] and *(6)*[7] served as reference substances. Hence the benzoxete structure *(3)* can be discounted.



(5)

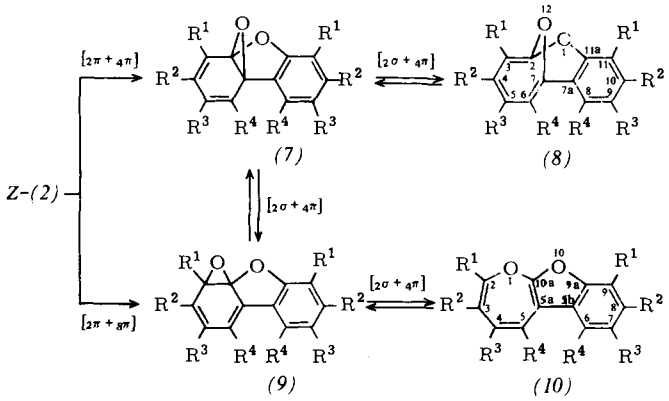
δ(CO) = 199.7 ppm



(6)

δ(CO) = 194.2 ppm

o,o'-Diphenoquinones are theoretically capable of undergoing a variety of valence isomerizations starting from either the *Z* or the *E* configuration. It follows from the ^{1}H- and ^{13}C-NMR spectra of the valence isomers that only those processes take place which involve *both CO groups* and lead to *asymmetric structures*. Thus, the only remaining possible intramolecular cycloadditions of these 14π electron systems are *Z-(2)*→*(7)*→*(8)* and *Z-(2)*→*(9)*→*(10)*:



This situation is reminiscent of oxygen-bridged [10]annulene[8]. Spectroscopic data oppose a benzene oxide structure and favor an oxepin structure *(8/10)*[9]: IR (KBr): resolved bands of medium intensity at 1600—1660 cm^{-1}.—^{1}H-NMR ($CDCl_3$): AB system of aromatic ring protons in *(8/10a)* at δ = 7.2 and 7.1 with $J_{1,3}$ = 2 Hz and AB system of the non-aromatic ring protons at δ = 6.4 and 5.5 with $J_{1,3} \leq 1$ Hz.—^{13}C-NMR ($CDCl_3$): 12 signals of expected multiplicity each for the sp^2 carbon atoms in the range $170.8 \geq \delta \geq 90.6$, which are not compatible with an epoxide structure but rather with the oxepin (ketene acetal) structures [C-3/C-5a: $100 \geq \delta \geq 96$; C-2/C-10a: $161 \geq \delta \geq 153$].

Thermal equilibria *(8)*⇌*(7)* and *(10)*⇌*(9)* can be ruled out on the basis of NMR measurements. However, the deoxygenation of *(8)* and *(10)* with triphenylphosphane or hydrogen iodide to the symmetrical dibenzofuran system[11] suggests a certain degree of reversibility. Differentiation between the two oxepin systems *(8)* and *(10)* is impossible by means of spectroscopic criteria alone. A decision in favor of the linearly annelated oxepino[2,3-*b*]benzofuran system *(10)* was provided by the X-ray analysis of *(8/10g)*. Whether the oxygen-bridged 2,7-epoxy-1-benzoxonins *(8)* can be formed on suitable substitution and under favorable reaction conditions and what mechanistic possibilities exist for the process *(1)*→*(10)* remain open questions.

Redetermination of the structure of the dehydrogenation products of *(1)* leads to the following conclusions:

1) To our knowledge, compounds *(8/10)* are the first oxepinobenzofurans to have been reported and belong to the very first oxepins ever isolated—*(8/10b)* in 1955[10].

2) The *o*-methylenecyclohexadienone partial structure in the *o,o'*-diphenoquinones does not tend to cyclize to benzoxete systems. This also indicates the possibility of reversion of a 2,4-cyclohexadienone to an oxepin ("reversal" of the NIH effect)[9a].

3) The mechanistic conclusions drawn from the benzoxete formulation and the structures of the formulated reaction products must be re-examined.

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(Z)-(2a), 65355-48-8; *(Z)-(2f)*, 65355-38-6; *(Z)-(2g)*, 65355-39-7; *(3a)*, 20026-75-9; *(3f)*, 65355-40-0; *(3g)*, 65355-41-1; *(5)*, 65355-42-2; *(6)*, 39117-89-0; *(8a)*, 65355-43-3; *(8f)*, 65355-44-4; *(8g)*, 65355-45-5; *(10a)*, 65355-46-6; *(10f)*, 65355-47-7; *(10g)*, 65355-49-9

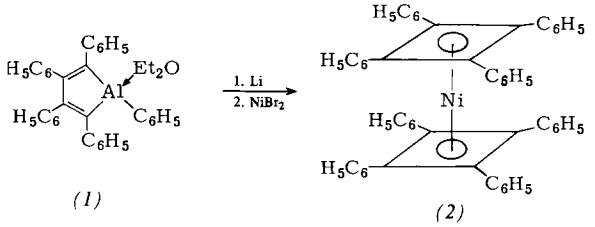
[1] *E. Müller, R. Mayer, B. Narr, A. Rieker, K. Scheffler*, Justus Liebigs Ann. Chem. *645*, 25 (1961); cf. also *P. Claus, P. Schilling, J. S. Gratzl, K. Kratzl*, Mh. Chem. *103*, 1178 (1972).
[2] a) *J. Baltes, F. Volbert*, Fette, Seifen, Anstrichm. *57*, 660 (1955); b) *E. Müller, H. Kaufmann, A. Rieker*, Justus Liebigs Ann. Chem. *671*, 61 (1964); c) *F. R. Hewgill, B. R. Kennedy*, J. Chem. Soc. *C 1966*, 362; *F. R. Hewgill, D. G. Hewitt, ibid. C 1967*, 726.
[3] a) *V. V. Karpov, M. L. Khidekel*, Zh. Org. Khim. *4*, 861 (1968); b) *H. D. Becker, K. Gustafsson*, J. Org. Chem. *42*, 2966 (1977); c) *H. Kaufmann*, Diplomarbeit, Universität Tübingen 1963; d) *H. Adolph, E. Müller*, unpublished.
[4] *H. D. Becker, K. Gustafsson*, Tetrahedron Lett. *1976*, 1705, 4883; *H. D. Becker*, J. Org. Chem. *34*, 1198 (1969); references cited therein.
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[8] *E. Vogel, M. Biskup, W. Pretzer, W. A. Böll*, Angew. Chem. *76*, 785 (1964); Angew. Chem. Int. Ed. Engl. *3*, 642 (1964); *F. Sondheimer, A. Shani*, J. Am. Chem. Soc. *86*, 3168 (1964).
[9] Cf. a) *A. Rieker, G. Henes, S. Berger*, Chem. Ber. *108*, 3700 (1975); b) *S. Berger, A. Rieker*, Org. Magn. Reson. *6*, 78 (1974).
[10] Unsubstituted oxepin: *E. Vogel, R. Schubart, W. A. Böll*, Angew. Chem. *76*, 535 (1964); Angew. Chem. Int. Ed. Engl. *3*, 510 (1964). 3-Benzoxepin: *K. Dimroth, H. Freyschlag*, Angew. Chem. *69*, 721 (1957). 1-Benzoxepin: cf. [8].

Bis(tetraphenylcyclobutadiene)nickel

By *Heinz Hoberg, Reinhild Krause-Göing*, and *Richard Mynott*[*]

The possibility of stabilizing cyclobutadiene by coordination to a transition metal was already pointed out as long ago as 1956[1], and soon afterwards *Criegee et al.* described the synthesis of the first monocyclobutadiene complex[2]. The isolation of bis(cyclobutadiene) complexes of the sandwich type, however, has so far not been reported in the literature[3].

We are able to show, on the basis of spectroscopic data and chemical behavior, that the compound of composition $C_8(C_6H_5)_8Ni$[4], obtained in *ca.* 5 % yield on reaction of (pentaphenyl)aluminacyclopentadiene *(1)* with Li metal and $NiBr_2$, is the octaphenyl derivative of bis(cyclobutadiene)nickel *(2)*.



(1) *(2)*

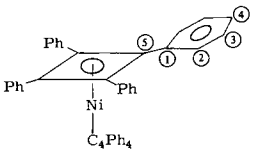
+ $C_{12}(C_6H_5)_{12}Ni_2$ + $C_8(C_6H_5)_8$ + ...

(2) crystallizes as well-formed small blue needles[5], m.p. 404 °C (dec).—The mass spectrum shows the molecular ion at $m/e = 770$ as well as characteristic fragments at $m/e = 414$ $[C_4(C_6H_5)_4Ni]$, 236 $[C_2(C_6H_5)_2Ni]$, and 178 $[C_2(C_6H_5)_2]$. The molecular weight of 765 (determined vaporimetrically in benzene) confirms the monomeric structure of the complex.

Only phenyl groups are detectable in the IR and ^{1}H-NMR spectra. In the UV spectrum (toluene) three bands are observed outside the phenyl absorption region (above 280 nm) at 295 ($\log\varepsilon = 4.8$), 370 (4.4), and 450 (4.7) nm. The band at 295 nm is of special significance regarding the assignment of structure for *(2)*, since an absorption maximum in the neighborhood of 300 nm is characteristic for cyclobutadiene-transition metal complexes[6]; the maximum at 450 nm corresponds to a d→d transition in the Ni complex.

The ^{13}C-NMR spectrum (Table 1) contains only five signals, thus indicating a high symmetry of the compound and ruling out a (tetraphenyl)nickelacyclopentadiene system[7].

Table 1. ^{13}C-NMR spectrum (25.2 MHz, Varian XL-100A-15) of complex *(2)* in [D$_8$]-tetrahydrofuran at 34 °C, reference signal β-CD$_2$ ($\delta_{TMS} = 25.3$).

	Signal	δ	Intensity
	1	133.8	small
	2, 3	128.9	2
		128.4	2
	4	127.0	1
	5	114.5	small

The signals at δ = 128.9, 128.4, and 127.0 in the ratio 2:2:1 lie in the region of protonated phenyl C atoms. With a small flip angle (α = 18°, pulse frequency 1.0 s) resonances are observed at δ = 133.8 and 114.5 which are to be assigned to the "quaternary" phenyl and cyclobutadiene C atoms (cf. Table 2).

Table 2. Chemical shifts of the four-membered ring C atoms in cyclobutadienenickel complexes.

Compound	Solvent	δ
$[C_4(C_6H_5)_4NiBr_2]_2$ [a]	$CDCl_3$	100.1
$[C_4(CH_3)_4NiCl_2]_2$ [b]	$CDCl_3$	108.0
(2)	[D$_8$]-THF	114.5

[a] *H. H. Freedman*, J. Am. Chem. Soc. *83*, 2194 (1961). [b] See [2a].

The low chemical reactivity of *(2)* is consistent with complete enclosure of the central Ni atom by the two tetraphenylcyclobutadiene ligands. Thus, the ligands cannot be replaced by CO, even at 110 °C and 1 atm. *(2)* is not attacked by boiling water within 24 h and is stable towards air over prolonged periods. In concentrated HNO_3 *(2)* is slowly oxidized, yielding mainly 1,2,3,4-tetraphenyl-2-butene-1,4-dione[8]. Mass spectrometric investigation reveals a further product with the molecular ion at $m/e = 372$ $[C_4(C_6H_5)_4O]$.

The cyclobutadiene system in *(2)* can be reduced or hydrogenated only with difficulty. No change is observed on treatment with $LiAlH_4$ in diethyl ether (35 °C, 48 h), Et_2AlH in toluene (110 °C, 48 h), H_2/Raney-Ni in hexane, or H_2/PtO_2 in ethanol (20 °C, 72 h). Metallic potassium, however, attacks *(2)* in liquid ammonia; hydrolysis affords predominantly 1,2,3,4-tetraphenylbutane and small amounts of 1,2,3,4-tetraphenylbutene.

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[**] ^{13}C-NMR analysis.

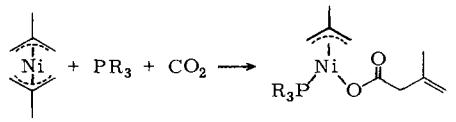
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Reactions of Carbon Dioxide with Allylnickel Compounds[**].

By *P. W. Jolly, Stefan Stobbe, Günther Wilke, Richard Goddard, Carl Krüger, Janine C. Sekutowski,* and *Yi-Hung Tsay*[*]

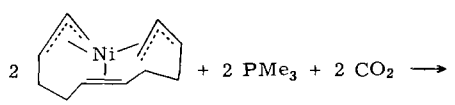
The fixation of carbon dioxide to transition metals has attracted considerable interest in recent years[1]. However, attempts to incorporate carbon dioxide in cooligomerization reactions have so far met with little success[2].

Although nickel(0) forms stable CO_2-complexes[3] and catalyzes the cyclo-cooligomerization of CO_2 with alkynes to substituted pyrones[2b], stoichiometric reactions of CO_2 with organonickel compounds have not yet been described. We have investigated the reaction of carbon dioxide with π-allylnickel complexes in order to gain an insight into possible catalytic reactions. Bis(η^3-methylallyl)nickel *(1)* reacts quantitatively with CO_2 in the presence of basic phosphanes to give carboxylates of type *(2)*:

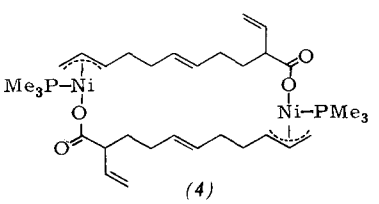


(1) *(2)*, R = CH_3, C_6H_{11}

The alkene-α,ω-bis(η^3-allyl)nickel complex *(3)*, which is formed as an intermediate in the cyclotrimerization of butadiene[4], reacts analogously with CO_2 in the presence of trimethylphosphane to give the dimer *(4)* (cryoscopic molecular weight determination).



(3)

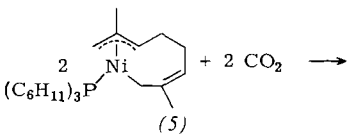


(4)

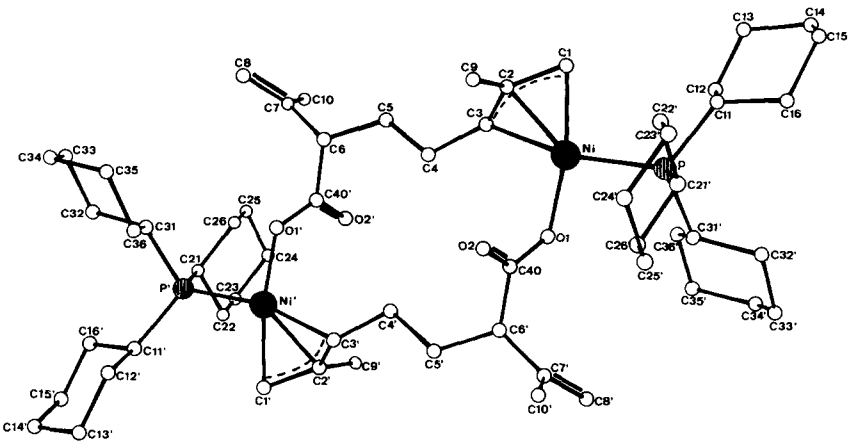
[*] Dr. P. W. Jolly, Dipl.-Chem. S. Stobbe, Prof. Dr. G. Wilke, Dr. R. Goddard, Dr. C. Krüger, Dr. J. C. Sekutowski, Dr. Y.-H. Tsay
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[**] This work was supported by the Deutsche Forschungsgemeinschaft.—Atomic parameters and Fo/Fc lists of the X-ray structure analyses are obtainable on request from the authors *(Goddard, Krüger, Sekutowski, Tsay)*.

The alkenyl-η^3-allyl(phosphane)nickel complexes, formed as intermediates in the Ni-catalyzed cyclodimerization of 1,3-dienes[5], also react smoothly with CO_2; the skeletal structure of the products, however, depends upon the diene employed.

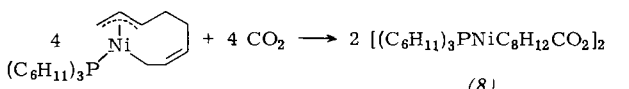


(5)

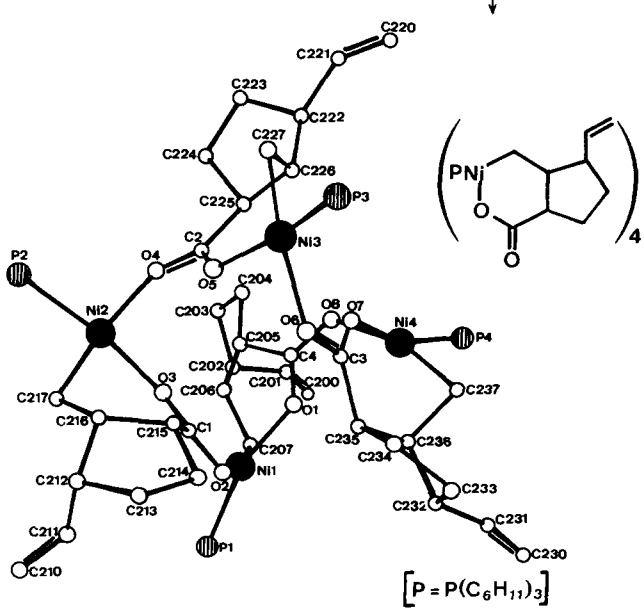


Treatment of *(5)* with CO_2 leads to *(6)*, which is structurally analogous to *(4)*. (*(5)* is prepared by reaction of isoprene with tricyclohexylphosphanenickel(0) and exists in two isomeric forms.) The structure of the dimer *(6)* was elucidated X-ray crystallographically[6].

The compound *(7)* from butadiene, corresponding to *(5)*, reacts with CO_2 to give the dimer *(8)*, which on heating in a toluene-acetone mixture rearranges into the tetrameric nickelalactone *(9)*. Complex *(9)* can also be prepared from $[(C_6H_{11})_3P]_2NiCO_2$ and butadiene. Its structure has been confirmed by X-ray structure analysis[7].



(7) *(8)*



These results are best explained as CO_2 insertion into an allylnickel σ-bond formed under the influence of the phosphane. Similar behavior is observed in the reaction of π-allylnickel complexes with isocyanates or SO_2[8].

Experimental

Synthesis of *(2)* ($R=C_6H_{11}$): Tricyclohexylphosphane (3.43 g, 12.3 mmol) is added at −30°C to a solution of *(1)*[9] (2.10 g, 12.4 mmol) in 10 ml toluene. After 2—3 h a stream of CO_2 is fed into the reaction vessel and the mixture stirred for 24 h. The yellow precipitate which separates after a short while is isolated at −30°C, washed twice with 10 ml ether, and dried under high vacuum at −10°C. Yield 4.25 (70%).—^{13}C-NMR (−50°C, D_8-toluene): δ = 40.5 (CH_2), 123.37 (CMe), 71.15 (d, J_{PC} = 19 Hz, CH_2) [η^3-Allyl]; 23.08, 23.56 (CH_3); 175.09 (C=O), 47.83 (CH_2), 143.69 (C=), 112.19 (=CH_2); 32.73, 29.83, 27.89, 26.76 (C_6H_{11}). IR (KBr): $\nu_{C=O}$ 1610 cm^{-1}.

Synthesis of *(6)*: Passage of CO_2 through a solution of *(5)* (4.75 g, 10 mmol) in ether or toluene leads to precipitation of *(6)* as a yellow solid. Yield 3.63 g (70%). IR (KBr): $\nu_{C=O}$ 1615 cm^{-1}.

Synthesis of *(9)*: A suspension of *(8)* in acetone heated to 60°C is diluted with toluene until complete dissolution. On cooling *(9)* precipitates as red crystals in almost quantitative yield.—IR (KBr): $\nu_{C=O}$ 1540 cm^{-1}.

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[7] Structural data for *(9)*: $a = 16.410(2)$, $b = 19.144(2)$, $c = 19.250(2)$ Å; $\alpha = 83.817(7)$, $\beta = 77.440(11)$, $\gamma = 74.423(8)°$; $Z = 2$; space group $P\bar{1}$; $R = 0.066$. Average bond lengths: Ni—P 2.146(4), Ni—O=C 2.007(7), Ni—O 1.920(7), Ni—C 1.945(10) Å. The four $C_9H_{12}O_2NiP(C_6H_{11})_3$ moieties are so arranged that a $(NiOCO)_4$ ring is formed. Each Ni atom is approximately square planar coordinated.
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Synthesis and Crystal Structure of a Methylenebis(diphenylphosphane) Complex of Silver Bromide Containing a Trigonal Bipyramidal Ag_3Br_2 Central Unit

By *Aref A. M. Aly, Dietmar Neugebauer, Olli Orama, Ulrich Schubert*, and *Hubert Schmidbaur*[*]

We recently reported a 2:1 complex of gold(I) chloride with methylenebis(diphenylphosphane)[1]. The ligand $CH_2(PPh_2)_2$ ("dpm") is characterized, like 1,8-naphthyridines[2] and some phosphorus ylides[3], by the fact that the metal atoms in its dinuclear coordination compounds lie in very close proximity to one another, thus favoring a transition to metal-metal bonding[4]. In dpm complexes of copper, aggregated groups are found to be present whose metal centers have a high tendency to fourfold coordination[5].

In the hitherto uninvestigated system silver(I) halide/dpm we have now discovered that specifically AgBr forms a 1:1 complex *(1)* in which formally three monomer units unite with dissociation of a $Br^{\ominus}$ ion to give a novel $Ag_3Br_2^{\oplus}$ structural moiety:

$$3\ AgBr + 3\ dpm \longrightarrow (dpm)_3Ag_3Br_2^{\oplus}Br^{\ominus} \qquad (1)$$

The product obtained on reaction of equimolar amounts of the reactants at 20°C in toluene crystallizes from CH_2Cl_2/pentane and shows the conductivity of a 1:1 electrolyte in CH_2Cl_2 ($17.2\,\Omega^{-1}\,cm^2\,mol^{-1}$ at 20°C, w.r.t. the trimer). The ^{1}H-NMR spectrum contains, besides the phenyl multiplet, only one complex signal for the CH_2 groups, indicating structural equivalence of all the dpm units. The structure and dimensions of the complex as deduced from an X-ray diffraction analysis[6] are depicted in Figure 1.

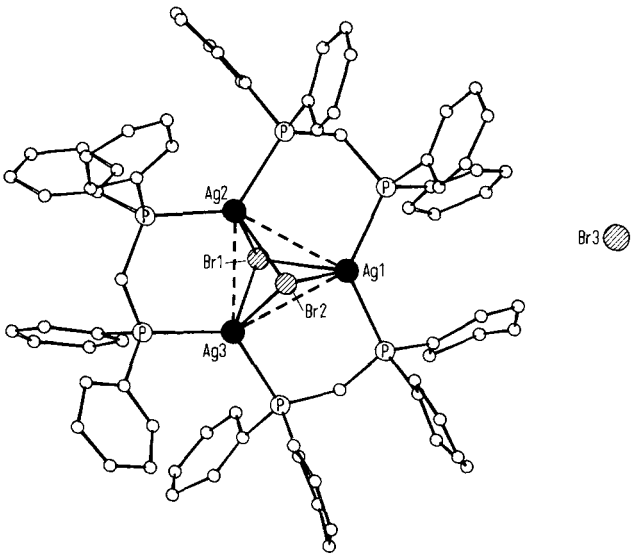


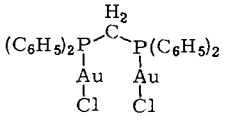
Fig. 1. Structure of crystalline complex *(1)*. Important bond lengths [pm] and angles [°]:

Ag1—Ag2	336.2(3)	Ag1—Br1	294.2(4)
Ag2—Ag3	319.2(3)	Ag1—Br2	278.4(4)
Ag1—Ag3	335.6(3)	Ag2—Br1	280.8(4)
		Ag2—Br2	283.8(4)
Ag—P	242(1) to 247(1)	Ag3—Br1	284.6(4)
		Ag3—Br2	279.0(4)
Ag1—Ag2—Ag3	61.5(1)	Ag1—Br1—Ag2	71.5(1)
Ag1—Ag3—Ag2	61.7(1)	Ag2—Br1—Ag3	68.7(1)
Ag2—Ag1—Ag3	56.7(1)	Ag1—Br1—Ag3	70.9(1)
		Ag1—Br2—Ag2	73.5(1)
		Ag2—Br2—Ag3	69.1(1)
		Ag1—Br2—Ag3	70.9(1)

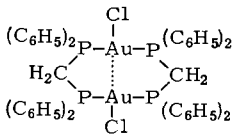
The silver atoms in *(1)* form an almost equilateral triangle; together with two approximately equidistant bromine atoms there arises a trigonal bipyramidal central unit. The sides of the Ag_3 triangle are singly bridged by a dpm ligand whose phenyl groups are twisted to avoid steric hinderance. In such an arrangement the silver atoms have coordination number

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[**] Alexander-von-Humboldt Fellow.

four, but the valence angles deviate somewhat from tetrahedral geometry. The two bromine atoms of the Ag_3Br_2 cage are each bound to all three silver atoms (sharp trigonal pyramids with small AgBrAg angles), while the third bromine atom is present as an isolated $Br^{\ominus}$ ion. All in all, the structure contains six $BrAg_2P_2C$ six-membered rings which are "condensed" *via* the Ag_3Br_2 skeleton in a chair or tub conformation. The metal-metal contacts of 319—336 ppm may still be regarded as non-bonding.



(2)



(3)

By way of comparison the Au—Au bond length in the gold complex *(2)*[1] is 335.1(2) pm, while the numerous analogous copper compounds so far described[5] have Cu—Cu distances of 2.546 to 3.281 pm; the cyclic derivative *(2)* has the shortest Au—Au contact of 296.2(1) pm[7].

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CAS Registry number:
(1), 65276-04-2

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[6] 2978 structure factors ($I \geq 3.1\,\sigma$, Syntex $P2_1/XTL$, ω-scan $2° \leq 2\theta \leq 45°$, $\lambda = 71.069$ pm), $R_1 = 0.068$; orthorhombic, space group $Pna2_1$, $Z = 4$, $a = 1909.8(1)$, $b = 2146.8(2)$, $c = 1858.1(2)$ pm, $V = 7618 \times 10^6$ pm^3.

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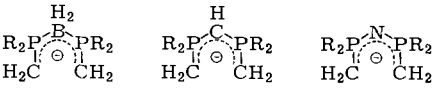
The Boratobis(dimethylphosphiniomethylide) Anion, a Novel Ligand System for Organometallic Compounds

By *Hubert Schmidbaur, Gerhard Müller, Ulrich Schubert*, and *Olli Orama*[*]

Despite their unusually interesting properties, phosphaneboranes *(A)* have hitherto hardly been investigated[1]. Especially remarkable is the thermal and chemical stability of the boratobis(trialkylphosphonium) salts *(B)*, which are soluble without decomposition in water and even stable toward mineral acids as well as alkalis[2].

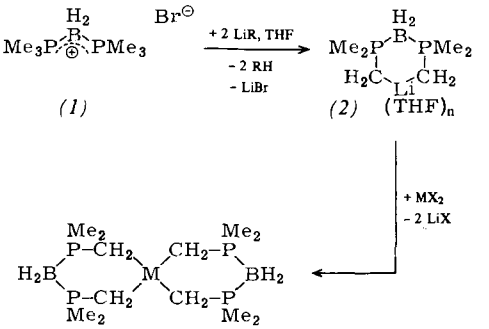
$R_3P{\rightarrow}BH_3$ *(A)* $[R_3P{\rightarrow}BH_2{\leftarrow}PR_3]^{\oplus}X^{\ominus}$ *(B)*

We have succeeded in functionalizing the alkyl groups of this cationic species such that the corresponding ylide anions *(C)* can be incorporated in organometallic compounds as novel ligands. The products closely resemble the isoelectronic methanido- and nitridobis(dialkylphosphiniomethylide) derivatives *(D)* and *(E)*, respectively[3].



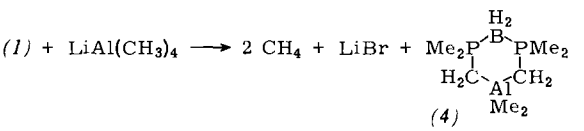
(C) *(D)* *(E)*

Boratobis(trimethylphosphonium) bromide *(1)*, which is readily accessible by a new one-pot method[4], rapidly reacts with two equivalents of *tert*- or *n*-butyllithium in tetrahydrofuran at -25 °C with loss of alkane to give the lithium complex of the ylide anion *(2)*, detectable in solution by NMR spectroscopy. Further reaction with metal halides leads to the chelate complexes *(3)* in good yields.



(1) *(2)* *(3a)*, M = Zn; *(3b)*, M = Cd; *(3c)*, M = Ni

Such metal boratobis(dimethylphosphiniomethylides) *(3)* are also obtainable by direct reaction of *(1)* with metal hydrides or alkyl derivatives, *e.g.* according to:



(4)

Composition and structure of the complexes were confirmed by elemental analysis, IR and NMR spectra, and by an X-ray structure analysis of *(3c)*[5]. Both the ^{1}H- as well as ^{11}B-, ^{13}C-, and ^{31}P-NMR spectra show equivalence of all Me_2PCH_2 groups in the molecules, and thus symmetrical bonding of the ligands to the metal. ^{1}H-, ^{13}C-, ^{111,113}Cd satellites confirm *e.g.* strong M-CH_2 interactions in *(3b)*. The only slightly altered BH_2 vibrations (IR) and BH-/BP coupling constants (NMR) compared to those observed in *(1)* indicate that the geometry of the CPBPC skeleton changes very little during formation of the complex so that the products can be assumed to contain largely strain-free six-membered rings, presumably in the chair conformation.

The properties of the new organometallic compounds *(3)* and *(4)* resemble those of the analogous derivatives of *(D)* and *(E)*. They are, however, thermally less stable if they contain readily reducible metals [*e.g. (3b)* and *(3c)*, but not *(4)*]. Here, the reducing effect of the borane function is still in evidence.

Procedure

A solution of butyllithium (20 mmol) in pentane or hexane is added dropwise with stirring at -25 °C to a suspension of *(1)* (2.45 g, 10 mmol) in tetrahydrofuran (50 ml). After 30 min, 5 mmol of metal halide (X = Cl, Br) is added and the reaction mixture stirred for a further 12 h at 20 °C. The

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solvent is then removed under vacuum and the residue taken up in benzene, filtered and crystallized from pentane/toluene. 0.68 g $ZnCl_2$ affords 2.7 g (69%) *(3a)* [m.p. 77°C], while 0.92 g $CdCl_2$ affords 2.84 g (65%) *(3b)* [m.p. 94°C], and 1.41 g $(Me_3P)_2NiCl_2$ affords 3.0 g (78%) *(3c)* [m.p. 90°C (dec.)]. *(3a)* and *(3b)* should preferably be sublimed. Spectroscopic data for $C_{12}H_{36}B_2CdP_4$ *(3b)*: IR (Nujol): νBH_2 2390 and 2350 cm^{-1}. ^1H-NMR (C_6H_6, TMS): $\delta CH_3 = 1.29$, "d", 6H, $J(HCP) = 9.75$ Hz; $\delta CH_2 = 0.05$, "d", 2H, $J(HCP) = 13.5$, $J(HCCd)$ 33.8 Hz[6]. ^{11}B-NMR (C_6H_6, $BF_3 \cdot Et_2O$): $\delta = -31.8$, $J(PB) = J(BH) = 92$ Hz[7]. $^{13}C\{^1H\}$-NMR (C_6D_6, TMS): $\delta CH_3 = 20.1$, AXX', $J(PC) = 43.9$ Hz; $\delta CH_2 = 1.18$, broad signal with satellites, $J(CCd) = 280.8$ Hz. $^{31}P\{^1H\}$-NMR (C_6H_6, 85% H_3PO_4): $\delta = -2.34$, q, $J(PB) = 100.7$ Hz.

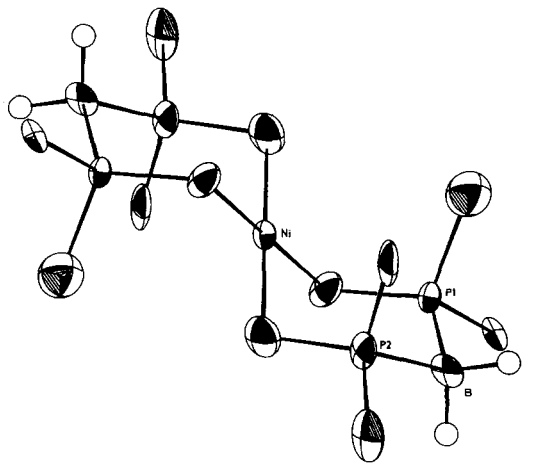


Fig. 1. Structure of crystalline nickel complex *(3c)* (H atoms of methyl and methylene groups are omitted for clarity). Averaged bond lengths [pm] and angles [°]:

Ni—C	199.4(9)
P—B	190 (1)
P—C (CH_2)	174.8(8)
P—C (CH_3)	181 (1)
C—Ni—C	90.0(3)
P—B—P	110.3(5)
B—P—C (CH_2)	112.3(4)
B—P—C (CH_3)	108.9(4)

A mixture of *(1)* (2.1 g, 8.6 mmol) and $LiAlMe_4$ (0.8 g, 8.5 mmol) is carefully warmed at a pressure of 10^{-1} torr. At 115°C evolution of gas is observed and a colorless liquid distils over which rapidly crystallizes. M.p. 70—71°C; dec. >200°C. $C_8H_{24}BAlP_2$ *(4)*: IR (Nujol): νBH_2 2410 and 2360 cm^{-1}. ^1H-NMR (C_6H_6, TMS): $\delta CH_3 = 1.35$, "d", 6H, $J(HCP) = 10.5$ Hz; $\delta CH_2 = 0.31$, "d", 2H, $J(HCP) = 18.0$ Hz; $\delta(AlCH_3) = -0.29$, s, 3H. ^{11}B-NMR (C_6H_6, $BF_3 \cdot Et_2O$): $\delta = -32.5$, $J(PB) = J(BH) = 97.5$ Hz[7]. $^{13}C\{^1H\}$-NMR (C_6D_6, TMS): $\delta CH_3 = 72.5$, AXX', $J(PC) = 21.3$ Hz; $\delta CH_2 = 67.7$, s (br). $^{31}P\{^1H\}$-NMR (C_6H_6, 85% H_3PO_4): $\delta = -4.65$, q, $J(PB) = 94.6$ Hz.

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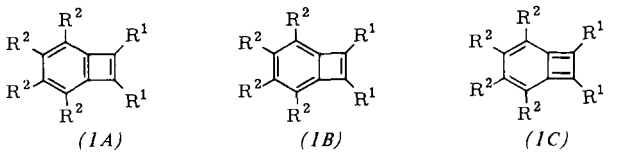
CAS Registry numbers:
(1), 65293-66-5; *(3a)*, 65293-65-4; *(3b)*, 65293-64-3; *(3c)*, 65293-63-2; *(4)*, 65293-62-1; ^{13}C, 14762-74-4; $LiAl(CH_3)_4$, 14281-94-8

[1] *G. W. Parshall* in *E. L. Muetterties:* The Chemistry of Boron and Its Compounds, Chap. 9. Wiley, New York 1967.
[2] *S. G. Shore, G. E. Ryschkewitsch* in *E. L. Muetterties:* Boron Hydride Chemistry. Academic Press, New York 1975, Chap. 3, 6.
[3] *H. Schmidbaur, O. Gasser*, Angew. Chem. *88*, 542 (1976); Angew. Chem. Int. Ed. Engl. *15*, 502 (1976); *H. Schmidbaur, H.-J. Füller, ibid. 88*, 541 (1976) and *15*, 501 (1976), resp.
[4] *G. Müller*, Diplomarbeit, Technische Universität München 1977.
[5] 1227 structure factors ($I \geq 3.3\sigma$, Syntex $P2_1/XTL$, ω-Scan, $2° \leq 2\theta \leq 48°$, $\lambda = 71.069$ pm), $R_1 = 0.05$; monoclinic, space group $P2_1/c$, $Z = 2$, $a = 629.5(1)$, $b = 2036.7(2)$, $c = 960.5(2)$ pm, $\beta = 119.21(8)°$, $V = 1075 \times 10^6$ pm^3.
[6] $A_6XX'A_6'$- and $A_2XX'A_2'$ splitting.
[7] Cf. *N. E. Miller, E. L. Muetterties*, J. Am. Chem. Soc. *86*, 1033 (1964). We are grateful to Dr. *B. Wrackmayer* and *L. Waldmann*, Universität München, for these spectra.

Molecular Structure of a Benzocyclobutadiene

By *Werner Winter* and *Henner Straub*[*]

In connection with the cyclobutadiene problem[1], cyclobutadienoid compounds such as the monobenzo-annelated derivative of [4]annulene are also of theoretical and preparative interest[2]. Besides the matrix isolation of the benzocyclobutadiene *(1)*, $R^1 = R^2 = H$, at 8 K[3], substituted benzocyclobutadienes isolable at room temperature have recently also been synthesized[4]. Such kinetically stabilized derivatives should permit the first experimental determination of the molecular geometry of a free benzocyclobutadiene. The derivative *(1)*[4b] was used for an X-ray structure analysis, since this yellow crystalline hydrocarbon is storable under nitrogen for months and the electronic system of such a derivative substituted only with alkyl groups can hardly be falsified compared to that of the parent compound ($R^1 = R^2 = H$). The bicyclic 8π system can be described by the three Kekulé structures *A*, *B*, and *C* (Kekulé indices: *A* 0.905, *B* 0.941, *C* 0.832)[5].



$R^1 = C(CH_3)_3$, $R^2 = CH_3$

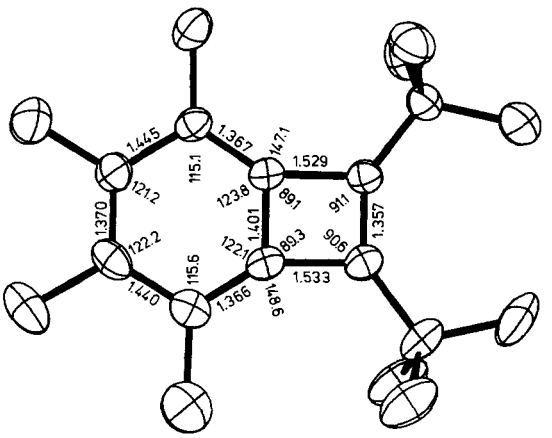


Fig. 1. ORTEP plot of *(1)*. The mean standard deviation for the bond lengths is 0.006 Å, for the bond angles 0.4°.

The crystal structure analysis[6] of *(1)* shows, within the limit of experimental error, that the benzocyclobutadiene moiety is planar. Further, since the C atoms bound directly to the bicycle deviate maximally by only about ±0.04 Å from this plane the whole system may be regarded as nearly planar.

The shortest C—C bond (1.36 Å) in the four-membered ring of *(1)* is to be interpreted as an isolated double bond;

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it is hardly influenced by the other 6π electrons of the six-membered ring. The longest bonds of the four-membered ring (1.53 Å) are somewhat longer than the usual single bonds of sp^2-hybridized C atoms. Both bond lengths are in good agreement with those of other cyclobutadiene systems[7] where, as also in *(1)*, the steric interaction of the bulky substituents could be responsible for stretching of the corresponding bonds of the four-membered ring. The shortest distance of only 2.11 Å between an H atom of a methyl group in the 3,6 position and the H atom of a methyl group of the *tert*-butyl moiety clearly shows that the substituents R^1 and R^2 in *(1)* approach each other to within the van der Waals distance.

The measured bond lengths in *(1)* rule out any noticeable participation of the resonance structure *(1C)*. The benzocyclobutadiene ground state is accordingly best described in terms of the two resonance structures *(1A)* and *(1B)*, the bond lengths in the six-membered ring suggesting greater participation of structure *(1B)*. Comparison of the experimentally determined bond lengths and angles of *(1)* with the calculated values of benzocyclobutadiene ($R^1=R^2=H$)[5,8] shows surprisingly good agreement. A large deviation is found only in the lengths of four-membered ring single bonds (calculated 1.49 Å), which can be attributed to the repulsive effect of the bulky substituents.

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[1] Review: *G. Maier*, Angew. Chem. *86*, 491 (1974); Angew. Chem. Int. Ed. Engl. *13*, 425 (1974); *S. Masamune*, Pure Appl. Chem. *44*, 861 (1975).
[2] Reviews: *M. P. Cava, M. J. Mitchell:* Cyclobutadiene and Related Compounds. Academic Press, New York 1967; *K. P. C. Vollhardt*, Fortschr. Chem. Forsch. *59*, 113 (1975).
[3] *O. L. Chapman, C. C. Chang, N. R. Rosenquist*, J. Am. Chem. Soc. *98*, 261 (1976).
[4] a) *H. Straub*, Angew. Chem. *86*, 412 (1974); Angew. Chem. Int. Ed. Engl. *13*, 405 (1974); b) Tetrahedron Lett. *1976*, 3513; Justus Liebigs Ann. Chem., in press; c) *F. Toda, N. Dan*, J. Chem. Soc. Chem. Commun. *1976*, 30; *F. Toda, K. Tanaka, ibid. 1976*, 1010; *K. P. C. Vollhardt, L. S. Yee*, J. Am. Chem. Soc. *99*, 2010 (1977).
[5] *M. Milun, N. Trinajstić*, Z. Naturforsch. *B 28*, 478 (1973); and references cited therein.
[6] Orthorhombic, space group $P2_12_12_12_1$; $a=10.042$, $b=10.885$, $c=16.146$ Å; $Z=4$; 1613 symmetry independent reflections [$I\geq 2\sigma(I)$], Nonius CAD-4, graphite monochromator, $Mo_{K\alpha}$; solution: non-centrosymmetric direct methods (SHELX-75, *G. M. Sheldrick*); refinement: $R=0.092$, $R_w=0.084$.
[7] *H. Irngartinger, H. Rodewald*, Angew. Chem. *86*, 783 (1974); Angew. Chem. Int. Ed. Engl. *13*, 740 (1974); *L. T. J. Delbaere, M. N. G. James, N. Nakamura, S. Masamune*, J. Am. Chem. Soc. *97*, 1973 (1975); cf. also *P. J. Garratt*, Pure Appl. Chem. *44*, 783 (1975).
[8] *M. J. S. Dewar, G. J. Gleicher*, Tetrahedron *21*, 1817 (1965).

Valence Isomeric η^2- and η^4-Cyclobutadiene-Rh^I Complexes

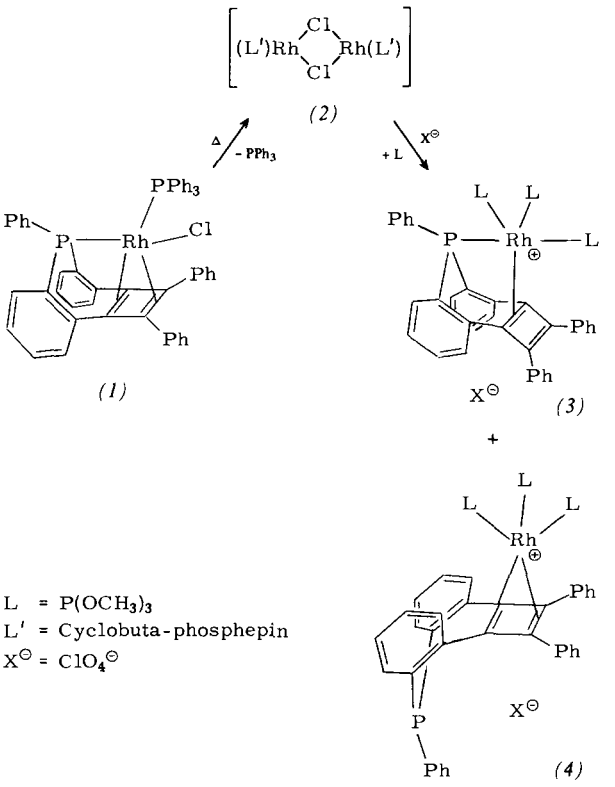
By *Werner Winter* and *Joachim Strähle*[*]

Transition metal complexes with η^4-cyclobutadiene ligands are well known. The isolation of iron complexes with η^2-coordinated cyclobutadiene was first described in 1974[1]; these unusual coordination compounds were characterized on the basis of spectroscopic data and their reaction products.

We now report the first synthesis of isomeric rhodium(I) complexes bearing variously coordinated cyclobutadiene.

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Heating of the violet Rh^I cyclobutadiene chelate complex *(1)*[2] in inert organic solvents (*e.g.* boiling xylene) leads, *via* cleavage of PPh_3, to an ocher-colored complex *(2)* which is insoluble in all the usual solvents:



L = $P(OCH_3)_3$
L' = Cyclobuta-phosphepin
$X^{\ominus}$ = $ClO_4^{\ominus}$

Apart from an elemental analysis, the insolubility of *(2)* precluded investigation of the complete structure or possible structural changes of the cyclobutadiene ligands. An attempt was therefore made to transform this product into a "soluble form" by cleavage of the Rh—Cl bridges. Treatment of *(2)* with an excess of trimethyl phosphite[3] in ethanol in the presence of $ClO_4^{\ominus}$ led within a few minutes to complete dissolution of the solid. Crystallization with CH_2Cl_2/ether gives mixture of red *(3)* and bright-yellow crystalls *(4)* (total yield >80%). Apart from differences in the usual analytical data (conductivity, IR, UV, NMR)[4], *(3)* and *(4)* differ characteristically in the $^{31}P\{^1H\}$-NMR spectrum: while *(3)* shows only signals of the Rh-coordinated P atoms, the spectrum of *(4)* also displays a singlet at $\delta=-0.7$ (H_3PO_4 ext; 36.43 MHz). This signal can be unequivocally assigned to a non-coordinated phosphepin P atom. The "inert gas rule" thus leads to formulation of a η^2- [for *(3)*] and a η^4-cyclobutadiene complex for *(4)*.

For confirmation of the structure we have carried out an X-ray structure analysis on *(3)*[5].

Figure 1 shows the essential structural features of *(3)*: the ligand arrangement at the rhodium approximately corresponds to a trigonal bipyramid, in which the phosphepin P atom occupies an apical position and the cyclobutadiene bond an equatorial position in the seven-membered ring. Strong back-bonding into π* orbitals of the seven-membered ring cyclobutadiene double bond leads to elongation of the C=C bond to 1.51 Å and pronounced angulation of the four-membered ring at the coordinated C atoms. The non-coordinated double bond of the four-membered ring, with a length of 1.34 Å, retains its double bond character.

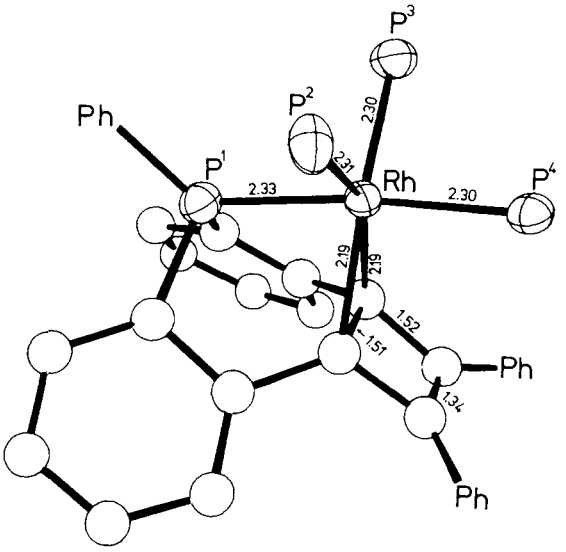
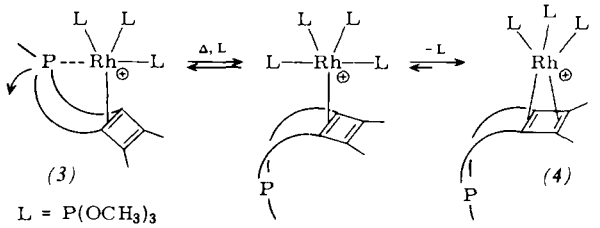


Fig. 1. Structure of the cationic complex *(3)* [phenyl- and (phosphite)OCH_3 substituents omitted for clarity]. The standard deviations for the Rh—P, Rh—C, and C—C bond lengths are 0.01, 0.02, and 0.03 Å, respectively.

The course of the reaction *(1)* → *(4)* reveals still further interesting points:

1) When the reaction of *(2)* with trimethyl phosphite is carried out at room temperature, *(3)* and *(4)* are formed in a ratio of about 1:1, while on prolonged heating under reflux (1 h) essentially only *(4)* is formed. However, since *(3)* is completely stable in boiling ethanol and is converted into *(4)* only in the presence of excess trimethyl phosphite, the transformation *(3)* → *(4)* most likely proceeds *via* a dissociative mechanism:



2) If, instead of *(2)*, the violet complex *(1)* is allowed to react with $P(OCH_3)_3$ at room temperature, only complexes of type *(3)* [L = PPh_3 and $P(OCH_3)_3$] are formed, and *no* complexes of type *(4)*. On the other hand, like *(2)*, *(1)* affords exclusively the complex *(4)* on prolonged refluxing.

The above findings lead to the following conclusions: on the one hand, the ring inversion of the dibenzo[*b*,*f*]-η-cyclobuta[*d*]phosphepin ligands in the transition *(3)* → *(4)* requires a surprisingly low free activation enthalpy [$\Delta G^{\neq}_{78\,°C}$ *ca.* 25—26 kcal·mol^{-1} with an estimated half-life of 15 min for *(3)*] in comparison to other non-complexed benzoannelated phosphepins (ΔG^{+}: 30–34 kcal·mol^{-1})[6]; on the other, either both conformers of this ligand must already be present in the insoluble complex *(2)*, or *(2)* forms a transition state in which the activation threshold for inversion is "undermined" by an intermediary phosphepin ring-opening.

The overall reaction sequence *(1)* → *(4)* has also been confirmed by X-ray structure analyses[4] of *(1)* and *(4)*.

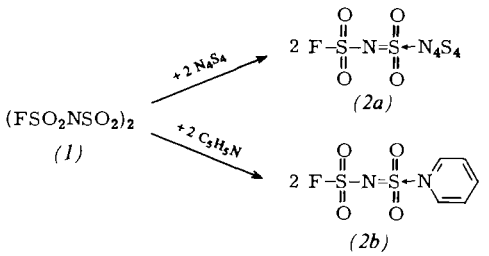
Received: November 18, 1977 [Z 866b IE]
German version: Angew. Chem. *90*, 142 (1978)

[1] *A. Sanders, W. P. Giering*, J. Am. Chem. Soc. *96*, 5247 (1974); *97*, 919 (1975).
[2] *W. Winter*, Angew. Chem. *87*, 172 (1975); Angew. Chem. Int. Ed. Engl. *14*, 170 (1975).
[3] Examples of bridge-rupturing reactions of olefin-Rh complexes with phosphanes or phosphites: *R. R. Schrock, J. A. Osborn*, J. Am. Chem. Soc. *93*, 2397 (1971).
[4] *W. Winter*, to be published.
[5] Monoclinic, space group C2/c; $a = 47.88$, $b = 10.62$, $c = 19.44$ Å, $\beta = 108.6°$; $Z = 8$; 2116 symmetry independent reflections [$I \geq 3\sigma(I)$; $-80°C$], Nonius CAD-4, $Mo_{K\alpha}$, graphite monochromator; solution: heavy atom method; refinement: $R = 0.10$ (Rh, P anisotropic); one phosphite atom is disordered. There is still another monoclinic modification of *(3)*, which is presently being investigated.
[6] *W. Winter*, Chem. Ber. *109*, 2405 (1976); Z. Naturforsch. *B31*, 1116 (1976).

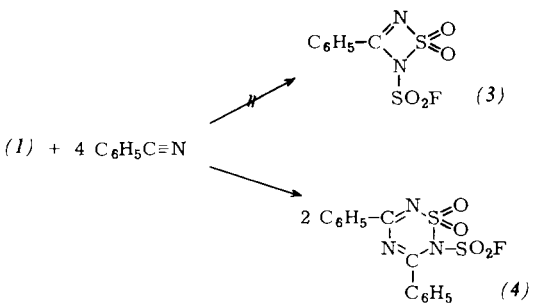
N-Fluorosulfonylsulfimide (*N*-(Fluorosulfonyl)sulfur Imide Dioxide)[**]

By *Herbert W. Roesky* and *Minoru Aramaki*[*]

N-Fluorosulfonylsulfimide could previously only be isolated as the cyclic dimer *(1)*[1]. Organic derivatives of sulfimide were postulated as intermediates in the dehydrohalogenation of the corresponding sulfamoyl chlorides[2]. We have now found that 1:1 adducts of *N*-fluorosulfonylsulfimide are readily accessible by reaction of *(1)* with tetrasulfur tetranitride or pyridine.



Lewis bases stabilize the monomeric *N*-fluorosulfonylsulfimide. The adducts *(2)* are interesting examples for the study of SN bond lengths as a function of coordination number. *(2a)* is a brick red crystalline solid, *(2b)* a white crystalline solid; they can be recrystallized from CH_2Cl_2 and stored without decomposition in dry air. Surprisingly, in the reaction of the dimeric sulfimide with benzonitrile



not the 1:1 adduct but the 1:2 adduct *(4)* is isolated. Presumably, the initially formed, strained three-membered ring *(3)* reacts further with benzonitrile to give *(4)*, a 1λ⁶,2,4,6-thiatriazine. Analogous reactions of *(1)* should lead to a wide variety of interesting new compounds.

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[**] This work was supported by Hoechst AG, Germany.

Procedure

(1)[1] (3.7 g, 11.6 mmol), diluted with CH_2Cl_2 (20 ml), is added dropwise to a solution of N_4S_4 (4.3 g, 23.4 mmol) in CH_2Cl_2 (450 ml). Dark-red *(2a)* immediately precipitates. The adduct is recrystallized from CH_3CN; yield 4.45 g (56 %), dec. pt. 105—110 °C; MS: $m/e = 283$ ($M^+ - NSO$); ^{19}F-NMR (in CH_3CN): $\delta = -55.8$ (s), rel. $CFCl_3$ ext.

For *(2b)*, prepared in an analogous way: M.p. 100 °C; MS: $m/e = 240$ (M^+); ^{19}F-NMR (in CH_3CN): $\delta = -53.5$ (s).

(1) (40 g, 12.4 mmol), diluted with CH_2Cl_2 (10 ml), is added dropwise to a solution of benzonitrile (5.1 g, 49.6 mmol) in CH_2Cl_2 (20 ml). The white crystalline reaction product *(4)* can be recrystallized from CH_3CN or C_6H_6; yield 5.5 g (60 %), m.p. 145 °C. MS: $m/e = 367$ (M^+, 100 %), 348 ($M^+ - F$, 2 %); ^{19}F-NMR (in C_6H_6): $\delta = -59.9$ (s).

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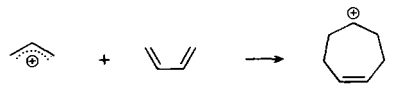
CAS Registry numbers:
(1), 60153-70-0; *(2a)*, 65392-47-4; *(2b)*, 65392-46-3; *(4)*, 65392-44-1; N_4S_4, 28950-34-7; $C_6H_5C{\equiv}N$, 100-47-0; C_5H_5N, 110-86-1

[1] *K. D. Schmidt, R. Mews, O. Glemser*, Angew. Chem. *88*, 646 (1976); Angew. Chem. Int. Ed. Engl. *15*, 614 (1976).
[2] *G. M. Atkins, Jr., E. M. Burgess*, J. Am. Chem. Soc. *94*, 6135 (1972).

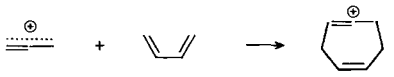
[4+3]-Cycloadditions of Allenyl Cations[**]

By *Herbert Mayr* and *Bärbel Grubmüller*[*]

Cycloadditions of allyl cations with dienes (Eq. A) have been studied in detail by *H. M. R. Hoffmann*[1].

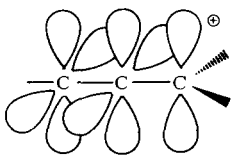


(A)



(B)

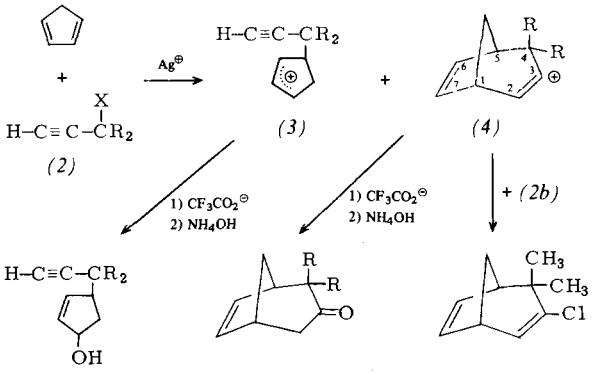
We now wish to report the first corresponding reactions of allenyl cations *(1)*, which proceed *via* formation of vinyl cations (Eq. B).



(1)

Treatment of a solution of propargyl bromide *(2a)*, X = Br, and cyclopentadiene in pentane with silver trifluoroacetate[2] and subsequent hydrolysis with aqueous ammonia affords a mixture of 85 % 4-(2-propynyl)cyclopent-2-en-1-ol *(5a)* and 15 % bicyclo[3.2.1]oct-6-en-3-one *(6a)* in 46 % yield. In a similar way reaction of 3-chloro-3-methyl-1-butyne *(2b)*, X = Cl, affords 28 % *(5b)*, 35 % *(6b)* and 37 % 3-chloro-4,4-dimethylbicyclo[3.2.1]octa-2,6-diene *(7b)* in a total yield of 50 %. Apart from insignificant amounts of high-molecular compounds, only the alcohols *(2)*, X = OH, were formed as by-products.

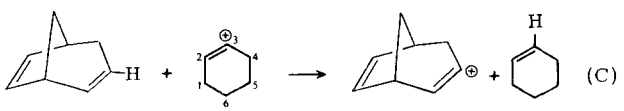
The cyclopentenols *(5)*, which occur as a mixture of diastereomers, can be identified by CrO_3-oxidation to the corresponding cyclopentenones. The spectroscopic data of the ketones *(6)* are in accord with data given in the literature[3]. The structure of *(7b)* was confirmed by ^{13}C-NMR and mass spectroscopy. The ^{1}H-NMR spectrum of this compound shows three olefinic protons [quartets at $\delta = 5.82$ and 6.30 (H^6 and H^7; $J_{67} = 6$, $J_{56} = J_{17} = 3$ Hz) as well as a doublet at $\delta = 6.03$ (H^2; $J_{12} = 7$ Hz)]; as expected on decoupling of the bridgehead protons H^1 and H^5 two doublets and a singlet are observed in the vinylic region. Similar ^{1}H-NMR spectra have been reported for other 3-halobicyclo[3.2.1]octa-2,6-dienes[4].



(a): R = H; *(b)*: R = CH_3

Formation of the products *(5)* to *(7)* can be explained in terms of intermediate allenyl cations *(1)* which are formed on reaction of $Ag^{\oplus}$ with *(2)*. Cyclopentadiene can attack *(1)* at the sp^2 carbon atom and thus give the alkynylcyclopentenyl cation *(3)*, which is intercepted by $CF_3CO_2^{\ominus}$. Hydrolysis of the resulting trifluoroacetate finally affords the alcohol *(5)*. A further possible explanation for the formation of *(3)* is that cyclopentadiene already attacks the alkynyl halide before the CX bond is completely cleaved.

The bicyclic products *(6)* and *(7b)* are derived from the vinyl cation *(4)*, which can be formed by concerted or stepwise cycloaddition of allenyl cation to cyclopentadiene. Reaction of *(4)* with $CF_3CO_2^{\ominus}$ affords a vinyl ester, whose hydrolysis leads to the ketone *(6)*. Alternatively, *(4)* can react with *(2b)* with formation of *(7b)* and liberation of a 1,1-dimethylallenyl cation. The corresponding reaction with *(2a)* is not observed, probably because the unsubstituted allenyl cation is insufficiently stabilized. Consistent with the proposed mechanism, *(7b)* is not formed if the concentration of *(2b)* is kept small by slow dropwise addition.



(8) *(4a)*, $\Delta H = 5.2$ kcal/mol (C)

According to MINDO/3 calculations[5] the vinyl cation *(4a)* is less stabilized than the monocyclic vinyl cation *(8)* by about 5 kcal/mol (Eq. C)—presumably because the optimized $C^2C^3C^4$ angle (146°) in *(4a)* deviates further from linear geometry than the corresponding angle (153°) in *(8)*[6]. For both vinyl cations *(4a)* and *(8)*, MINDO/3 calculations

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indicate a delocalization of the positive charge by the hyperconjugative effect of the C^1C^2 and C^4C^5 bonds.

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CAS Registry numbers:
(1), 1724-44-3; *(2a)*, X = Br, 106-96-7; *(2b)*, X = Cl, 1111-97-3; *(3a)*, 65404-80-0; *(3b)*, 65404-81-1; *(4a)*, 65404-93-5; *(4b)*, 65404-94-6; *cis-(5a)*, 65404-95-7; *trans-(5a)*, 65404-96-8; *cis-(5b)*, 65404-97-9; *trans-(5b)*, 65404-98-0; *(6a)*, 3721-60-6; *(6b)*, 22940-29-0; *(7b)*, 65404-99-1; *(8)*, 60690-49-5; cyclopentadiene, 542-92-7

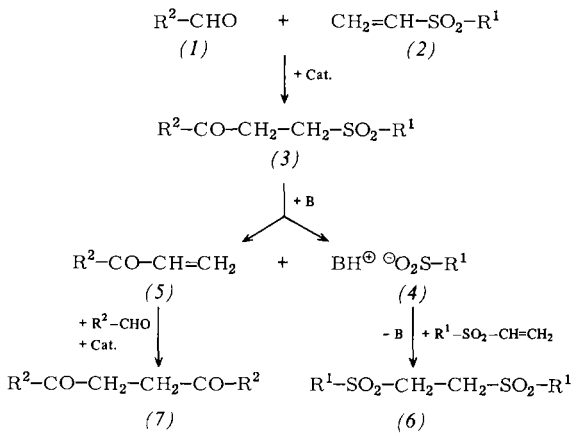
[1] *H. M. R. Hoffmann*, Angew. Chem. *85*, 877 (1973); Angew. Chem. Int. Ed. Engl. *12*, 819 (1973).
[2] On the effect of the silver counterion cf. *H. M. R. Hoffmann, G. F. P. Kernaghan, G. Greenwood*, J. Chem. Soc. *B 1971*, 2258.
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A New Preparation of Symmetrical γ-Diketones[1]

By *Hermann Stetter* and *Hans-Jürgen Bender*[*]

The thiazolium salt-catalyzed addition of aliphatic, aromatic, and heterocyclic aldehydes[2] to activated double bonds can also be extended to α,β-unsaturated sulfones.

Surprisingly, however, the product is not the expected γ-keto sulfone but a 1:1 mixture of γ-diketone and γ-disulfone. We explain this result as a consequence of cleavage of the γ-keto sulfone *(3)* into sulfinate *(4)* and vinyl ketone *(5)*. A further molecule of aldehyde *(1)* adds to the vinyl ketone to form the symmetrical γ-diketone *(7)*, which is actually isolated. The sulfinate ion reacts with unconsumed vinyl sulfone *(2)*, giving the γ-disulfone *(6)* which can likewise be isolated.



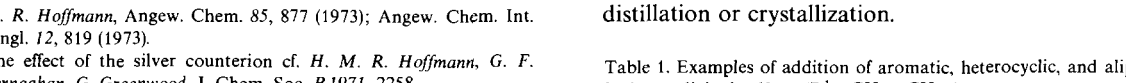
The reaction has been observed for several aryl vinyl sulfones and can be exploited preparatively when divinyl sulfone (R^1 = CH=CH_2) is used as double bond component since separation of γ-disulfone and γ-diketone is then a simple operation. Moreover, the ratio of aldehyde to vinyl sulfone can then be limited to 2:1.

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The reactions compiled in Table 1 were performed under the following reaction conditions:

In the case of aliphatic aldehydes, the aldehyde (0.2 mol) and divinyl sulfone (0.1 mol) are jointly added dropwise to a hot stirred solution of thiazolium salt[2] (0.02 mol) and sodium acetate (0.04 mol) in ethanol (200 ml); aromatic and heterocyclic aldehydes can be immediately added to the reaction solution so that only the double bond component has to be added dropwise. The mixture is stirred for 12 h under reflux, poured into water, and then extracted with chloroform to give the corresponding γ-diketone which is purified by distillation or crystallization.

Table 1. Examples of addition of aromatic, heterocyclic, and aliphatic aldehydes to divinyl sulfone (R^1 = CH_2=CH–).



R^2	Yield [%] [a]	B.p. [°C/torr] M.p. [°C]	Ref. (m.p., b.p.)
n-C_3H_7	43	110/7	[3]: 53.5/0.1
n-C_4H_9	56	75/0.3	[4]: 53
n-C_5H_{11}	53	98/0.3	[5]: 100/0.4
n-C_6H_{13}	63	68	[6]: 68.5
n-C_7H_{15}	61	76	
2-Furyl	75	131	[7]: 131
2-Thienyl	48	130—131	[8]: 131—132
Phenyl	46	143—144	[9]: 144

[a] Since no intermediates were isolated the yields are based upon the amount of diketone *(7)*, *i.e.* calculated over all three reaction steps.

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(1) (R^2 = n-C_3H_7), 123-72-8; *(1)* (R^2 = n-C_4H_9), 110-62-3; *(1)* (R^2 = n-C_5H_{11}), 66-25-1; *(1)* (R^2 = n-C_6H_{13}), 111-71-7; *(1)* (R^2 = n-C_7H_{15}), 124-13-0; *(1)* (R^2 = 2-furyl), 98-01-1; *(1)* (R^2 = 2-thienyl), 98-03-3; *(1)* (R^2 = phenyl), 100-52-7; *(2)* (R^1 = CH_2=CH–), 77-77-0; *(6)* (R^1 = CH_2=CH–), 39690-70-5; *(7)* (R^2 = n-C_3H_7), 22633-21-2; *(7)* (R^2 = n-C_4H_9), 15982-65-7; *(7)* (R^2 = n-C_5H_{11}), 22633-22-3; *(7)* (R^2 = n-C_6H_{13}), 54277-01-9; *(7)* (R^2 = n-C_7H_{15}), 65378-70-3; *(7)* (R^2 = 2-furyl), 22111-14-4; *(7)* (R^2 = 2-thienyl), 13669-05-1; *(7)* (R^2 = phenyl), 495-71-6

[1] Addition of Aldehydes to Activated Double Bonds, Part 18.—Part 17: *H. Stetter, J. Nienhaus*, Chem. Ber., in press.
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Olefin Metathesis with Polymer-Bound Tungsten Complexes[1]

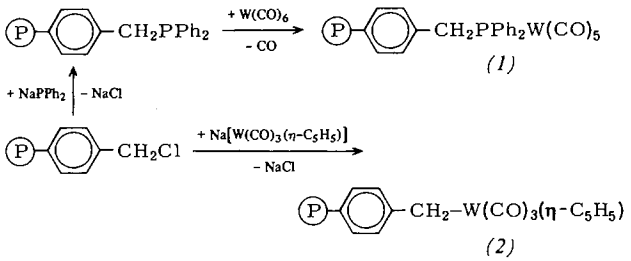
By *Siegfried Warwel* and *Peter Buschmeyer*[*]

Ready separation of homogeneous transition metal catalysts from the substrate and catalyst recycling processes are of decisive importance in industrial applications. A possible solution of such problems is proved by the so-called heterogeniza-

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tion of transition metal complexes, *i.e.* their linkage to insoluble inorganic or organic carriers.

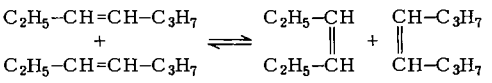
We now describe the first use of polymer-bound carbonyltungsten complexes for the metathesis of open-chain monoolefins. The tungsten-polymer complexes *(1)* and *(2)*



(1)

(2)

prepared according to *Pittman et al.*[2] from a commercially available *Merrifield* resin[3] effect, after activation with iBuAlCl$_2$/O$_2$, selective metathesis of *trans*-3-heptene to give an equilibrium mixture.



Compound *(1)* or *(2)* was then separated from cocatalyst and the olefins by filtration. After washing with methanol and drying at 25 °C *in vacuo* the complex catalysts could be re-used.

The tungsten complex *(1)* coordinated to the polymeric matrix proved to be a storage catalyst: the polymeric phosphane ligand serves as reservoir for a coordinatively unsaturated tungsten species which is displaced by the alkylaluminum compound and then forms a homogeneous catalyst for the metathesis reaction. Compound *(1)* can therefore be re-used only in a limited number of runs (Figure 1).

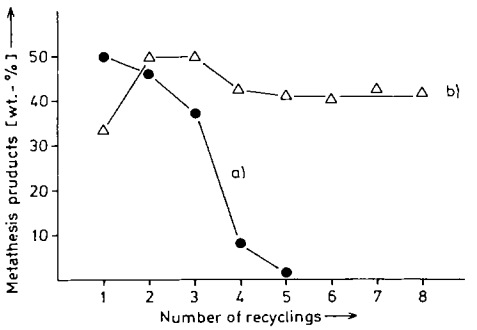


Fig. 1. Metathesis of *trans*-3-heptene with polymer-bound tungsten complex catalysts—conversion as a function of the number of recyclings on use of a) *(1)*/iBuAlCl$_2$/O$_2$ and b) *(2)*/iBuAlCl$_2$/O$_2$ in the ratio W:Al:O$_2$:olefin = 1:4:2:700 (22—24 °C; 60 min per metathesis reaction).

In contrast, the tungsten complex *(2)* covalently bonded to the polymer combined the advantages of homogeneous and heterogeneous metathesis catalysts, *i.e.* activity and selectivity under mild conditions on the one hand, and ready removal from the reaction solution, regeneratability, and especially the possibility of frequent re-use, on the other hand. On repeated recycling the activity profile of *(2)* corresponds to that of heterogeneous catalysts; low initial activity (experiment 1) is followed by a maximum (experiments 2 and 3) which then adjusts to a constant value (experiments 4 to 8).

The scope of the catalysts was examined with other open-chain olefins having an internal double bond (*cis*- and *trans*-hexene, mixture of *n*-octene isomers) and confirmed; co-metathesis of these olefins with vinylcyclohexene was also possible. The development of further complex catalysts with polymeric ligands could prove of value in elucidating the mechanism of olefin metathesis.

Metathesis of trans-3-heptene with (2)/iBuAlCl$_2$/O$_2$

Compound *(2)* (60 mg, containing 9.3 % W) is placed in a dry *ca.* 10 ml-capacity Schlenk tube. After repeated evacuation and flushing with argon, *trans*-3-heptene (2.06 g, 21 mmol) containing 15 wt% of methylcyclohexane as GC standard as well as isobutylaluminum dichloride (0.12 mmol; 0.24 ml of a 0.5 M solution in chlorobenzene) and O$_2$ (1.4 ml, 0.06 mmol) are added from syringes; the contents of the vessel are mixed with a magnetic stirrer. After 60 min a sample of the reaction solution is treated with small amount of CH$_3$OH and analyzed by gas chromatography (3-heptene 67.0, 3-hexene 14.6, 4-octene 18.4 wt %). Compound *(2)* is separated from the other compounds by filtration, washed with *ca.* 20 ml of CH$_3$OH, dried at 25 °C *in vacuo*, and re-used for metathesis.

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CAS Registry numbers:
trans-3-heptene, 14686-14-7; 3-hexene, 592-47-2; 4-octene, 592-99-4; diethenylbenzene, polymer with ethenylbenzene, 9003-70-7; NaPPh$_2$, 4376-01-6; W(CO)$_6$, 14040-11-0; Na[W(CO)$_3$(η-C$_5$H$_5$)], 12107-36-7; i-BuAlCl$_2$, 1888-87-5

[1] Olefin Metathesis, Part 5. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 4: *S. Warwel, A. Aivasidis*, Chem.-Ztg. *101*, 361 (1977).

[2] *G. O. Evans, C. U. Pittman Jr., R. McMillan, R. T. Beach, R. Jones*, J. Organomet. Chem. *67*, 295 (1974); *C. U. Pittman Jr., R. F. Felis, ibid. 72*, 399 (1974).

[3] Chloromethylated polystyrene (Cl content: 5.1 %) crosslinked with 2 % of divinylbenzene available from the Merck-Schuchardt company.

Quantitative Resolution of Enantiomers of *trans*-2,3-Epoxybutane by Complexation Chromatography on an Optically Active Nickel(II) Complex[**]

By *Volker Schurig* and *Waldemar Bürkle*[*]

Enantiomers often differ characteristically in their pharmacological and physiological properties (substrate-receptor interaction). It is therefore advantageous to be able to directly determine the enantiomer composition of chiral substrates rapidly and quantitatively, without having to resort to derivatization and measurement of optical rotation, and to gain information about the kinetic and thermodynamic factors of chiral differentiation.

The method of choice for this purpose is the gas chromatographic resolution of enantiomers on optically active stationary phases by selective interactions between hydrogen bonds, as introduced by *Gil-Av* and *Feibush*[1].

We recently reported the first chromatographic resolution of a chiral olefin by enantiospecific π-complexation on a rhodium(I) compound *(1)*[2] and thus showed that the rapid and reversible ligand-metal coordination interaction can have the necessary thermodynamic parameters for "chiral recognition" in GC systems.

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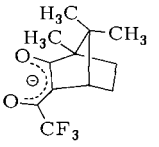
We have now demonstrated the previously postulated[3] resolution of enantiomers of chiral σ-donor substrates containing elements of groups 5 and 6 on optically active dimeric nickel(II) bis(3-trifluoroacetyl-1*R*-camphorate) *(2)*, with the quantitative separation of dissymmetric (C_2) *E*-dimethyloxirane (*trans*-2,3-epoxybutane) *(4a)* as example. While we were

$Rh(CO)_2$(tfac-1*R*-Cam) *(1)*

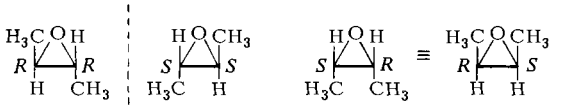
$[Ni(tfac\text{-}1R\text{-}Cam)_2]_2$ *(2)*

$Eu(tfac\text{-}1R\text{-}Cam)_3$ *(3)*

tfac-1*R*-Cam =



carrying out our investigations *Golding et al.* reported the (incomplete) resolution of the enantiomers of methyloxirane (epoxypropane) *(5)* on the europium(III) complex *(3)*; separation of *(4a)*, however, was not observed[4].



trans (*threo*)
racemic
"homochiral"

(4a)

cis (*erythro*)
meso
"heterochiral"

(4b)

On chromatography of *(4a)* on a 200-m capillary column loaded with 1*R*-*(2)* in squalane, the mirror image isomers appear as two sharply separated peaks (Fig. 1). Racemic *(5)* is resolved into its antipodes by 1*R*-*(2)* as well. The surprisingly high resolution of *(4a)* ($\alpha = 1.27$, 50 °C) permits its separation also in shorter time with shorter length columns[5]. Successful resolution was demonstrated by use of the racemic nickel complex 1*S*,1*R*-*(2)*, where peak coalescence occurs in the case of *(4a)* and *(5)*. Separation of the diastereomers *(4a)* and *(4b)* (Fig. 1) could also be achieved with the highly selective complex *(2)*. In accordance with the greater tendency of *cis*- over *trans*-2-butene to undergo π-complexation with *(1)*[6] the *cis* compound *(4b)* also exhibits a much stronger coordination with *(2)* than does the *trans*-diastereomer. It is noteworthy that the observed enantiomer differentiation, whose Gibbs-Helmholtz parameters[3] are still being investigated, is already achieved by enantiospecific "one-point" coordination interaction[7].

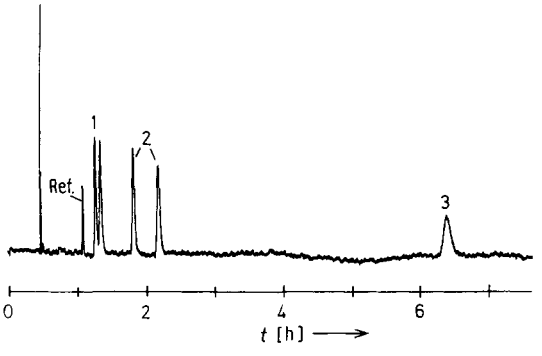


Fig. 1. Resolution of enantiomers and diastereomers of *(4)* and *(5)* by complexation chromatography on 1*R*-*(2)* (0.15 *m* in squalane) at 50 °C.
1, Peak splitting (1:1) for *(5)*; 2, peak splitting (1:1) for *(4a)*; 3, *(4b)*; reference standard: cyclohexane. Column: 200 m × 0.5 mm nickel capillary, carrier gas: 2.1 ml/min N_2, split 1:50.

The method described here, which does not necessitate the preparation of derivatives or purification of substances, is suitable for the determination of enantiomer composition in the study of racemization, retention, or inversion, as well as asymmetric induction in the formation or ring-opening of chiral substrates such as *(4a)* and *(5)*. The GC method thus surpasses the NMR method (use of chiral "shift" reagents, *e.g. (3)*) in simplicity, accuracy, and sensitivity (amount of substance required 10^{-9} g!). The nickel complex 1*R*-*(2)* is readily accessible[8].

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[4] *B. T. Golding, P. J. Sellars, A. K. Wong*, J. Chem. Soc. Chem. Commun. *1977*, 570. We thank the authors for information prior to publication.
[5] Packed columns [4] appear to be unsuitable, since polar substrates tend to show peak tailing on the support (chromosorb) in the presence of squalane.
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Substituted Bicyclohexyls—A New Class of Nematic Liquid Crystals[**]

By *Rudolf Eidenschink, Dietrich Erdmann, Joachim Krause*, and *Ludwig Pohl*[*]

We have found that *trans,trans*-4'-alkylbicyclohexyl-4-carbonitriles *(3)* exhibit nematic phases (Table 1) whose transition temperatures to the isotropic phase are considerably higher than those of the recently described 4-(*trans*-4-alkylcyclohexyl)benzonitriles[1].

This result does not conform to the molecular-statistical theory of *Maier* and *Saupe*[2], according to which the nematic-isotropic transition temperature should be essentially proportional to the molecular polarizability anisotropy. Rather it becomes clear that shape anisotropy can make a considerable—hitherto disregarded—contribution to the stability of nematic phases[3].

In order to prepare *(3)*, 4-(*trans*-4-alkylcyclohexyl)benzoic acids *(1)*, obtained by a known procedure[1], are hydrogenated over palladium/activated charcoal (10% Pd) in glacial acetic acid. The resulting mixture of saturated stereoisomeric carboxylic acids is treated with sulfinyl chloride by the same method as used in the preparation of *trans*-4-alkylcyclohexanecarboxylic acids[4]. After hydrolysis of the acid chlorides, the pure *trans,trans*-4'-alkylbicyclohexyl-4-carboxylic acids *(2)* (Table 1) were obtained by repeated recrystallization from light petroleum (boiling range 50 to 70 °C). These acids could be converted, in the usual way, into the corresponding nitriles by brief action of sulfinyl chloride, reaction with ammonia solution, and dehydration of the resulting amides with $POCl_3$. The structures of *(3a)* to *(3c)* have been confirmed by elemental analysis, and IR and mass spectrometry.

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[**] This work was supported by the Federal German Ministry of Research and Technology.

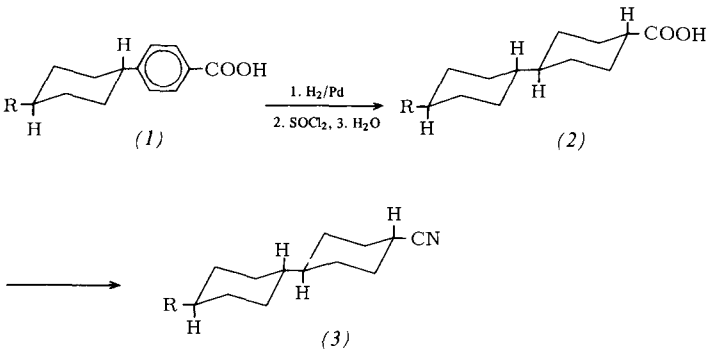


Table 1. Nematic ranges of compounds *(2)* and *(3)*.

	R	Yield [%]	M.p. [°C]	Clear point [°C]
(2a)	n-C_3H_7	34	197	246
(2b)	n-C_5H_{11}	39	224	243
(2c)	n-C_7H_{15}	45	230	238
(3a)	n-C_3H_7	56	58	80 [a]
(3b)	n-C_5H_{11}	60	62	85 [b]
(3c)	n-C_7H_{15}	67	71	83

[a] Monotropic transitions at 18, 44, 48 (smectic-smectic), and 57 °C (smectic-nematic).
[b] Monotropic transitions at 43 °C (smectic-smectic) and 52 °C (smectic-nematic).

The new compounds *(3)* are photochemically, electrochemically, and thermally stable. In keeping with their molecular structure, they fail to show any UV absorption above 200 nm. They have a positive dielectric anisotropy whose magnitude lies between 3 and 4, an optical anisotropy of <0.1, and, as the first monomeric thermotropic-nematic class of liquid crystals, a negative diamagnetic anisotropy[5]. As a result of these properties, they can serve as anisotropic solvents for the measurement of polarized absorption and fluorescence spectra in the entire UV range and also permit the recording of high-resolution NMR spectra with rotating samples, thus giving rise to resolutions comparable with those in isotropic solution (signal half-width <1 Hz)[6].

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(1a), 65355-29-5; *(1b)*, 65355-30-8; *(1c)*, 65355-31-9; *(2a)*, 65355-32-0; *(2b)*, 65355-33-1; *(2c)*, 65355-34-2; *(3a)*, 65355-35-3; *(3b)*, 65355-36-4; *(3c)*, 65355-37-5

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[3] *W. H. de Jeu*, personal communication.
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[5] *L. Pohl, R. Eidenschink, J. Krause, G. Weber*, to be published.
[6] *L. Pohl, R. Eidenschink*, to be published.

Preparation of *cyclo*-Hexasulfur Oxide, S_6O[1]

By *Ralf Steudel* and *Jürgen Steidel*[*]

Among the homocyclic sulfur oxides S_nO, S_8O[2] and S_7O[3] have so far been prepared pure while the extremely unstable species S_5O[4] has only been detected in solution. We have now succeeded in preparing the first derivative of *cyclo*-hexasulfur, *viz.* S_6O.

S_6O is formed on oxidation of S_6 by trifluoroperacetic acid at -10 to -20 °C in dichloromethane:

$$S_6 + CF_3CO_3H \rightarrow S_6O + CF_3CO_2H$$

Depending upon the reaction conditions, two different products of the same composition are formed. α-S_6O arises when S_6 reacts with the peroxy acid at -20 °C within 2 h in the molar ratio 1:1.2 and the oxidation product is precipitated after a further 5 h by addition of pentane and cooling. Recrystallization gives a 5 % yield of orange transparent spearhead-shaped crystals which undergo spontaneous decomposition to polymeric sulfur with evolution of SO_2 at 39 °C. At 25 °C decomposition is almost complete within 2 h; at -50 °C no decomposition can be detected even after several weeks. The composition corresponds exactly to the formula S_6O. In the mass spectrum the molecular ion appears with low intensity at $m/e = 208/210$[5]. Vacuum pyrolysis affords the product S_2O characteristic of polysulfur oxides.

According to the Raman spectrum[5] α-S_6O contains small amounts of S_6 in solid solution which cannot be removed by repeated recrystallization. Attempts to achieve complete oxidation of S_6 by working at a higher temperature (-10 °C) and with an excess of peroxy acid ($S_6 : CF_3CO_3H = 1:2.2$) led to isolation of β-S_6O which likewise still contained traces of S_6. β-S_6O forms dark orange, transparent prismatic or truncated pyramidal crystals which decompose at 34 °C. Its stability corresponds to that of α-S_6O. Both oxides are moderately soluble in CS_2, CH_2Cl_2, and $CHBr_3$.

The Raman spectra of α- and β-S_6O show characteristic differences in wave numbers and intensities; in particular a number of normal modes are split to doublets in the case of α-S_6O (Table 1). In solution in CS_2 or $CHBr_3$ both modifications give identical IR spectra (Table 1). Model calculations using the force constants[6] of S_6 and S_8O show that the spectra can be assigned on the basis of a structure analogous to that of S_8O with a chair-shaped S_6 ring and an exocyclic oxygen atom.

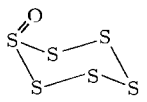
Table 1. Normal modes of S_6O in the solid and dissolved state (cm^{-1}; Raman intensities in parentheses).

Raman α-S_6O	Raman β-S_6O	IR (in $CHBr_3$)	Assignment
1092(14)	1102(12)	1112 vs	ν(SO)
499(55)	499(51)	506 vw	ν(SS)
486(4)	488(14)	494 w	ν(SS)
463(12)	463(20)	462 vw	ν(SS)
445(19)			ν(SS)
440(20)	441(27)	438 m	
414(37)	406(29)	414 m	δ(SSO)
370(19)	371(11)	365 m	δ(SSO)
341(19)			ν(SS)
329(100)	320(100)	320 w	
298(22)	296(35)		ν(SS)
293(18)			
279(28)	279(60)		δ(SS)
236(47)	236(23)		δ(SS)
193(87)	203(41)		δ(SS)
182(49)	194(57)		δ(SS)
162(5)	175(24)		τ(SS)
131(10)	160(8)		τ(SS)

The differences between α- and β-S_6O are probably not due to differences in molecular structure (*e.g.* with axial or

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equatorial oxygen) but to different lattice symmetries, with S_6 occupying a small number of lattice sites in both cases.



The synthesis of S_6O raises the number of known nonpolymeric sulfur oxides to 11 (SO, SO_2, SO_3, SO_4, S_2O, S_2O_2, S_3O_9, S_5O, S_6O, S_7O, S_8O).

Procedure

CF_3CO_3H solution: $(CF_3CO)_2O$ (8.1 ml) is added at 0°C to a vigously stirred emulsion of H_2O_2 (1.67 g, 80 %) in CH_2Cl_2 (91 ml; purified by column chromatography on basic Al_2O_3). The mixture is warmed to 25°C and stirring is continued until no droplets of H_2O_2 can be seen.

S_6O: In order to prepare α-S_6O, S_6 (4.18 g; β-S_6O: 5.75 g S_6) is dissolved in highly pure CH_2Cl_2 (2.3 l) at 0°C and protected from the action of light. At −20°C (−10°C) 66.1 ml (167 ml) of the CF_3CO_3H solution is added dropwise with stirring over 2 h (15 min). The reaction solution is stirred for 5 h (3 h) and, after addition of *n*-pentane (1.5 l, −20°C), cooled to −78°C, whereupon 1.13 g of a crude product containing α-S_6O (0.64 g of crude product containing β-S_6O) crystallize. Recrystallization from 900 ml (350 ml) purified CH_2Cl_2 affords 241 mg of α-S_6O (78 mg of β-S_6O) with a slight residual trace of S_6 (solid solution).

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CAS Registry numbers:
S_6O, 65366-47-4; S_6, 13798-23-7; CF_3CO_3H, 359-48-8

[1] Part 55 of "Sulfur Compounds".—Part 54: *R. Reinhardt, R. Steudel, F. Schuster*, Angew. Chem. *90*, 55 (1978); Angew. Chem. Int. Ed. Engl. *17*, 57 (1978).

[2] *R. Steudel, M. Rebsch*, Z. Anorg. Allg. Chem. *413*, 252 (1975); *R. Steudel, J. Latte*, Angew. Chem. *86*, 648 (1974); Angew. Chem. Int. Ed. Engl. *13*, 603 (1974).

[3] *R. Steudel, T. Sandow*, Angew. Chem. *88*, 854 (1976); Angew. Chem. Int. Ed. Engl. *15*, 772 (1976).

[4] *W. Genz, P. W. Schenk*, Z. Anorg. Allg. Chem. *379*, 300 (1970).

[5] Mass spectrometer Varian MAT 311 A, electron energy 70 eV, sample temp. 40°C, ion source temp. 100°C; Raman spectrometer Cary 82, Krypton laser 647.1 nm, sample temp. −90°C.

[6] *R. Steudel*, Spectrochim. Acta *31 A*, 1065 (1965).

Molecular and Crystal Structure of an Organocyclotriarsane[**]

By *Gerhard Thiele, Gerd Zoubek, Helmut A. Lindner*, and *Jochen Ellermann*[*]

Organocycloarsanes $(RAs)_n$ with $n=4$, 5 and 6 are well known[1], and their structure has been elucidated by X-ray structure analyses on some representative examples[2]. The first compound of this type to be synthesized containing a three-membered As ring—also known to be a structural unit in the As_4 molecule and its derivatives[3]—was 4-methyl-1,2,6-triarsatricyclo[2.2.1.$0^{2,6}$]heptane *(1)*[4]. We have now been able to synthesize *(1)* in good yields and to investigate its crystal and molecular structures.

The colorless, monoclinic crystals of *(1)* [space group C2/m; unit cell with $a=1101.5(6)$, $b=907.2(5)$, $c=829.6(5)$ pm, $\beta=104.9(6)°$, $Z=4$] show a distorted cubic close packing of $CH_3C(CH_2As)_3$ molecules. In the crystal these are situated in a plane of symmetry, but there is little deviation from the C_{3v} symmetry expected for the free molecule. In the As_3 ring the As—As bond lengths are almost equal (Fig. 1) and

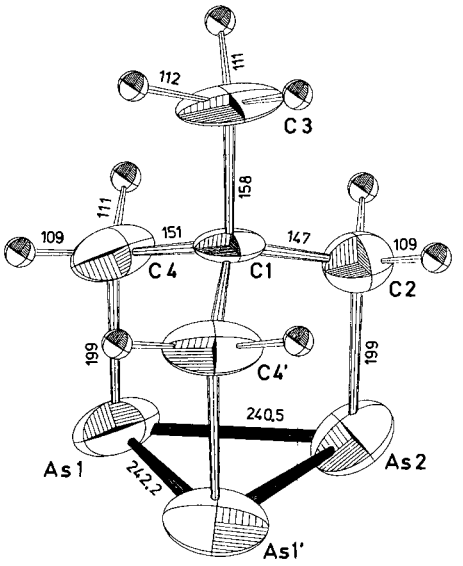


Fig. 1. Structure of the molecule *(1)*, with bond lengths in [pm]; standard deviation for *d*(As—As) 0.5, for *d*(As—C) 2, for *d*(C—C) 2.5, and for *d*(C—H) 4 pm. A plane of symmetry passes through the atoms C1, C2, C3 and As2. The angle at the C atoms deviate at most by about 1° from the tetrahedral angle; other angles: As1—As1'—As2 = 59.7(2), As1—As2—As1' = 60.5(2), As1—As1'—C4' = 90.2(6), As2—As1—C4 = 90.7(6), As1—As2—C2 = 90.1(6)°.

comparable to those found in As_4 (244 pm[3a]). Remarkably the organic moiety is oriented almost perpendicularly to the As_3 plane, the As—As—C angles being *ca.* 90°. The reasons for this observed contraction in comparison[8] to the similarly built As_4S_3 molecules of the two modifications of dimorphite, whose corresponding angles (about 101°)[5] approach the tetrahedral angle, might largely be geometric. The basal plane of the trigonal $CH_3C(CH_2)_3$ pyramid has edges of almost the same length as the As_3 triangle, while that of the AsS_3 pyramid in As_4S_3 is much larger (*ca.* 340 pm). The shortest intermolecular As—As distances (388 pm) deviate very little from the sum of the van der Waals radii, so that only slight interactions between the molecules are to be expected. In accordance with this are the color and thermal behavior of the crystals.

Experimental

$CH_3C(CH_2AsI_2)_3$[6] (1.5 g, 1.42 mmol) is dissolved in 20 ml dry peroxide-free tetrahydrofuran (THF) under nitrogen as protective gas. 2—3 ml of this solution is poured onto 1 g (40 mmol) of granulated sodium and the mixture carefully warmed with stirring until reduction with frothing sets in; the color of the mixture first turns dark-red and then changes to green-yellow. The rest of the THF solution is added dropwise within 15 min without further warming and then filtered free of excess Na, NaI and decomposition products. After removal of the THF at 20°C, *(1)* is separated from any

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[**] Contributions to the Chemistry of Polyfunctional Ligands, Part 42. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Hoechst AG, Frankfurt am Main.—Part 41: *J. Ellermann, N. Geheeb, G. Zoubek, G. Thiele*, Z. Naturforsch. *B 32*, 1271 (1977).

NaI present by sublimation (90°C/10^{-5} bar); yield 305 mg (73 %).

Crystals suitable for the X-ray structure analysis were grown by cooling a 0.03 M solution of *(1)* in THF to −30°C. After decanting off the mother liquor, the crystals were washed twice at room temperature with 2 ml petroleum ether. A crystal in the form of a monoclinic prism was measured on a four-circle diffractometer (Philips PW 1100, $Mo_{K\alpha}$ radiation; graphite monochromator) ($3° \leqq \theta \leqq 24°$). For the structure determination (program system SHELX[7]) 2656 measurements were available, giving a set of 671 independent data. Refinement (for all heavy atoms with an anisotropic temperature factor, for the H atoms with a common isotropic temperature factor) led to an R value of 0.088.

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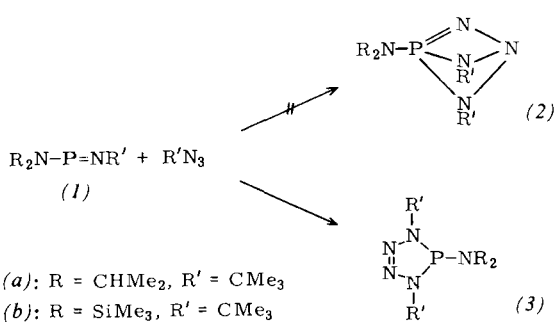
CAS Registry numbers:
(1), 52196-03-9; $CH_3C(CH_2AsI_2)_3$, 52196-02-8

[1] *L. R. Smith, J. L. Mills*, J. Organomet. Chem. *84*, 1 (1975); and references cited therein.
[2] *N. Mandel, J. Donohue*, Acta Crystallogr. *B 27*, 467 (1971); *A. Tzschach, V. Kiesel*, J. Prakt. Chem. *313*, 259 (1971); *J. H. Burns, J. Waser*, J. Am. Chem. Soc. *79*, 859 (1957); *K. Hedberg, E. W. Hughes, J. Waser*, Acta Crystallogr. *14*, 369 (1961).
[3] a) *L. R. Maxwell, S. B. Hendricks, V. M. Mosley*, J. Chem. Phys. *3*, 699 (1935); b) *A. S. Foust, M. S. Foster, L. F. Dahl*, J. Am. Chem. Soc. *91*, 5631 (1969).
[4] *J. Ellermann, H. Schössner*, Angew. Chem. *86*, 646 (1974); Angew. Chem. Int. Ed. Engl. *13*, 601 (1974).
[5] *H. J. Whitfield*, J. Chem. Soc. Dalton Trans. *1973*, 1737; J. Chem. Soc. *A 1970*, 1800.
[6] *J. Ellermann, H. Schössner, H. A. Lindner*, unpublished results.
[7] *G. Sheldrick*, University Chemical Laboratory, Cambridge UK.
[8] *Note added in proof* (January 16, 1978): The recently determined structure of the cluster anion As_3^{3-} can also be used for comparison: *W. Schmettow, H. G. von Schnering*, Angew. Chem. *89*, 895 (1977); Angew. Chem. Int. Ed. Engl. *16*, 857 (1977).

Structure of the 1:1 Adduct of Aminoiminophosphane and *tert*-Butyl Azide

By *Siegfried Pohl, Edgar Niecke*, and *Hans-Günther Schäfer*[*]

We recently reported the addition of *tert*-butyl azide to an aminoiminophosphane and suggested that the product obtained had the structure of an imino-bridged triaza-λ^5-phosphetine *(2a)*[1]. A crystal structure analysis of the analogously prepared 1:1 adduct of bis(trimethylsilyl)amino-*tert*-butyliminophosphane and *tert*-butyl azide, however, is not consistent with the structure *(2b)* but with that of a tetraaza-λ^3-phospholine *(3b)*. It would now seem that the compound previously characterized as *(2a)* should more correctly be described as having the structure *(3a)*.



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The cyclic silylaminophosphane *(3b)* is a colorless solid which can be isolated in pure form after removal of aminodiiminophosphorane, formed as liquid by-product in the reaction[2], and several recrystallizations from a little toluene. Its structure has been confirmed by a complete X-ray structure analysis[3] (cf. Fig. 1).

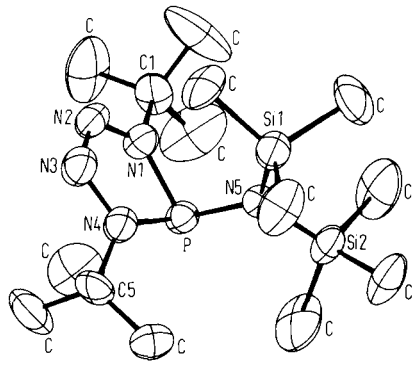


Fig. 1. Molecular structure of 1,4-di-*tert*-butyl-5-bis(trimethylsilyl)amino-Δ^2-tetraazaphospholine *(3b)* in the solid (without H atoms, 50 % probability vibration ellipsoids).

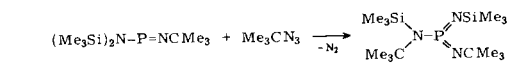
Coordination and bonding at the phosphorus are not unusual and thus provide no indicative evidence for the extreme high-field shift of the ^{31}P-NMR signal. The five-membered ring is almost planar (angle between the normals to the planes through N1, N2, N3, N4, and N1, P, N4: 7.8°). The considerable difference between the two P—N5—Si angles (*ca.* 15°) can be attributed to steric interaction between the bis(trimethylsilyl)amino group and the *tert*-butyl groups (cf. Ref.[4]).

The ^{1}H- and ^{13}C{^{1}H}-NMR spectra show the three and four groups of signals to be expected for the different stereochemistry of the two trimethylsilyl groups[5]. In temperature dependent ^{1}H-NMR measurements between 25 and 100°C there is no noticeable change in signal multiplicity—a finding which, in combination with the structural data, would indicate steric fixation of the $(Me_3Si)_2N$ groups. The different configurations of the two Me_3Si groups and the different P—N—Si bond angles account for the large difference in the P—C and P—H coupling constants. A surprising feature in comparison to the previously known phosphanes containing the PN_3 unit is the upfield shift of the ^{31}P-NMR signal ($\delta = 36.4$, H_3PO_4 ext.), which for *(3a)* ($\delta = 23.9$[1]) was erroneously regarded as indicating fourfold coordination of the phosphorus. The cause of this shielding of the ^{31}P nucleus in tetraaza-λ^3-phospholines is still unclear.

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CAS Registry numbers:
(1a), 63950-84-5; *(1b)*, 54760-90-6; *(2a)*, 63950-85-6; *(2b)*, 65392-63-4; *(3a)*, 65392-64-5; *(3b)*, 65392-65-6; *tert*-butyl azide, 13686-33-4

[1] *E. Niecke, H. G. Schäfer*, Angew. Chem. *89*, 817 (1977); Angew. Chem. Int. Ed. Engl. *16*, 783 (1977).
[2] A competing reaction according to



E. Niecke, W. Flick, H. G. Schäfer, unpublished.
[3] The crystals are monoclinic $P2_1/n$, with $a = 1010.5(4)$, $b = 1493.3(7)$, $c = 1472.0(6)$ pm, $\beta = 92.10(3)°$, $V = 2220 \times 10^6$ pm^3, $Z = 4$. The structure was solved by direct methods. The refinement with structure factors from 2420 observed reflections [$I \geqslant 1.96\,\sigma(I)$] converged to an unweighted R value of 8.3 % (Syntex $P2_1$ diffractometer, Syntex XTL program).
[4] *E. Niecke, W. Flick, S. Pohl*, Angew. Chem. *88*, 305 (1976); Angew. Chem. Int. Ed. Engl. *15*, 309 (1976).
[5] 30 % in CH_2Cl_2 (^{1}H-NMR) and 60 % in $CDCl_3$ (^{13}C-NMR) rel. TMS int.: $\delta = 0.10$, 0.30, $^4J_{HP} = 0.1$, 3.6 Hz [$N(SiMe_3)_2$]; 1.45 [$NCMe_3$] and $\delta = 3.5$, 4.5, $^3J_{CP} < 0.2$, 16.6 Hz [$N(SiC_3)_2$]; 30.9, 56.7, $^3J_{CP} = 7.8$, $^2J_{CP} = 15.6$ Hz [NCC_3], respectively.

Crystal Structure of Sb_2O_5 [**]

By *Martin Jansen*[*]

Although the $Sb_2O_3/Sb_2O_5/H_2O$ system has been repeatedly studied by various methods[1], the nature of antimony(v) oxide has remained a matter of controversy because there is still a lack of sufficient knowledge about the phases occurring therein and their homogeneity ranges. In the course of new preparative and structural studies it has now been possible to determine the crystal structures of Sb_2O_5 and $Sb_2O_5 \cdot {}^3/_5 H_2O \equiv Sb_5O_{12}OH \cdot H_2O$[2].

The space group, lattice constants, and number of formula units per unit cell of Sb_2O_5 are: C2/c; $a = 1455$, $b = 478.2$, $c = 2289$ pm, $\beta = 90°$; $Z = 20$. Since reflections hkl with odd l can only be found for $l = 5$, and then only at low intensity, a subcell can be given with $a' = a$, $b' = b$, $c' = c/2$. It therefore follows that of the 3347 independent reflections measured (Philips PW 1100 automatic four-circle diffractometer, Mo-K_α, graphite monochromator, ω scan) only 1243 have net intensities greater than $1.5\,\sigma(I)$. All the crystals examined were microtwinned; structural elucidation was accomplished by Patterson and Fourier methods.

In contrast to As_2O_5[3] all the cations in Sb_2O_5 are in octahedral coordination ($d_{Sb-O} = 191$—208 pm), and the coordination numbers of oxygen towards antimony are 2 and 3. Figure 1 shows the crystal structure of Sb_2O_5, looking along [010]. "Layers" of rutile structure linked by common octahedral corners are seen. The relationship to the rutile type becomes all the clearer on imagining the rutile structure to be completely regenerated by a series of translations, as indicated by the arrows in Figure 1. The possibility of deriving crystal structures of oxides having the composition MO_{2+x} from the rutile type has already been discussed at length[4].

Sb_2O_5 is the first pentoxide of a main group element whose principles of coordination and connection correspond to those of an analogous oxide of a subgroup element, *viz.* B—Nb_2O_5[5].

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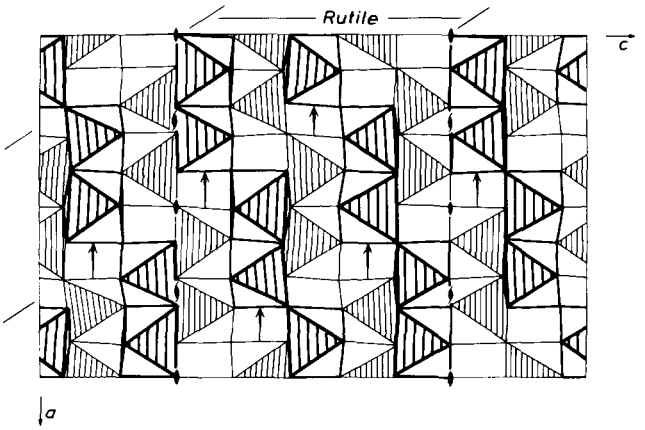


Fig. 1. Crystal structure of Sb_2O_5, as viewed along [010].

Experimental

Our results confirm earlier reports[1b] that Sb_2O_5 cannot be prepared under normal pressure.

In order to prepare Sb_2O_5, antimony(III) oxide (analytical grade, Merck) was heated in a steel autoclave (corundum finger crucible, closed with a corundum stopper but not gas tight); the autoclave (volume 20 ml, sample volume including corundum crucible 6 ml) was charged with liquid oxygen (9 ml). Reaction conditions: duration 3 weeks; temperature 700 °C.

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German version: Angew. Chem. 90, 141 (1978)

[1] a) *G. Jander, A. Simon*, Z. Anorg. Allg. Chem. *127*, 68 (1923); *A. Simon, E. Thaler, ibid. 161*, 113 (1927); *H. E. Swanson, M. I. Cook, E. H. Evans, J. H. de Groot*, Nat. Bur. Stand. (U.S.) Circ. 539-*10*, 10 (1969); b) *D. J. Stewart, O. Knop, C. Ayasse, F. W. D. Woodhams*, Can. J. Chem. *50*, 690 (1972); *E. Schwarzmann, H. Rumpel, W. Berndt*, Z. Naturforsch. *B32*, 617 (1977).
[2] *M. Jansen*, to be published.
[3] *M. Jansen*, Angew. Chem. *89*, 326 (1977); Angew. Chem. Int. Ed. Engl. *16*, 314 (1977); Z. Anorg. Allg. Chem., in press.
[4] *S. Andersson, J. Galy*, J. Solid State Chem. *1*, 576 (1970).
[5] *H. Schäfer, R. Gruehn, F. Schulte*, Angew. Chem. *78*, 28 (1966); Angew. Chem. Int. Ed. Engl. *5*, 40 (1966); *F. Laves, W. Petter, H. Wulf*, Naturwissenschaften *51*, 633 (1964).

ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

Human chorionic gonadotropin, its receptor and mechanism of action, is the title of paper by *O. P. Bahl*. Chorionic gonadotropin consists of two non-covalently linked subunits which are only effective in complex form. The protein contains carbohydrate chains. These can be removed stepwise; however, the products so obtained are still capable of binding to the receptor. Although they inhibit the accumulation of *cyclo*-AMP effected by the native chorionic gonadotropin they promote production of steroid in the target cell. This finding would suggest the possible existence of other carriers of hormone action apart from *cyclo*-AMP. The receptor for the hormone could be isolated from radioactively labeled corpus luteum membranes, thus permitting investigation of the mode of action of the hormone on a molecular basis. [Human Chorionic Gonadotropin, its Receptor and Mechanism of Action. Fed. Proc. *36*, 2119—2127 (1977); 56 references]
[Rd 990 IE]

Reactions in which inorganic pyrophosphate replaces ATP as a source of energy are described by *H. G. Wood*. In biochemistry it is generally believed that pyrophosphate is an end product of metabolism serving at most to make preceding reactions

irreversible once it has been hydrolyzed. However, on the basis of recent knowledge this viewpoint is gradually losing favor. Although the energy of hydrolysis of pyrophosphates is less than that of ATP it is still sufficient to make synthesis reactions possible. In the organisms *Entamoeba hystolytica* and *Propionibacterium shermanii*, enzymic reactions have been discovered in which pyrophosphate plays a role. Examples

$$\text{Pyrophosphate} + \text{oxaloacetate} \rightleftharpoons \text{phosphoenol pyruvate} + \text{phosphate} + CO_2 \quad (1)$$

$$\text{Pyrophosphate} + \text{AMP} + \text{phosphoenol pyruvate} \rightleftharpoons \text{pyruvate} + \text{ATP} + \text{phosphate} \quad (2)$$

$$\text{Pyrophosphate} + \text{fructose-6-phosphate} \rightleftharpoons \text{phosphate} + \text{fructose-1,6-diphosphate} \quad (3)$$

are the reactions *(1)* to *(3)*, which are catalyzed by a carboxytransphosphorylase, a pyruvate-phosphate-dikinase and a pyrophosphate-phosphofructokinase, respectively. [Some Reactions in which Inorganic Pyrophosphate Replaces ATP and Serves as a Source of Energy. Fed. Proc. *36*, 2197—2205 (1977); 52 references]

[Rd 991 IE]

The structure and function of *Escherichia coli* ribosomes are described in an article by *H. G. Wittmann*. The ribosome consists of a 30S subunit, composed of 21 proteins and a 16S RNA, and a 50S subunit made up of 34 proteins and 5S and 23S RNA. All components have been isolated and characterized, and in some cases the sequences are already known. The overall structure of the subunits is presently under investigation. The methods employed in these investigations include crosslinking of neighboring components, fragmentation of subunits, localization of binding sites of proteins to the RNA, neutron scattering, fluorescence spectroscopy and immuno-electron microscopy. The latter method affords the most useful information. Protein biosynthesis at the ribosomes consists in several steps; the participation of the individual components of the ribosomes is investigated with the aid of affinity-labeling and reconstitution. [Structure and Function of *Escherichia coli* Ribosomes. Fed. Proc. *36*, 2075—2080 (1977); 105 references]

[Rd 992 IE]

The structural basis for the variation in redox potentials of cytochromes is discussed by *G. R. Moore* and *R. J. P. Williams*. Structural studies on proteins are usually aimed at gaining knowledge of the biological properties of proteins on a molecular basis. In the case of redox potentials of cytochromes the determining factors are mainly the charges of the axial ligands and their donor and acceptor strengths for electrons. In contrast changes in the spin state of the central metal ion and steric factors are of secondary importance. [Structural Basis for the Variation in Redox Potential of Cytochromes. FEBS Lett. *79*, 229—232 (1977); 24 references]

[Rd 993 IE]

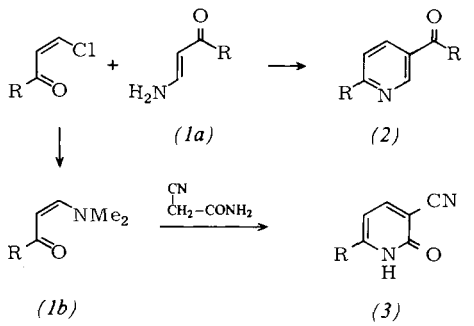
The biosynthesis of melittin, the venom of the honey bee, is the subject of a report by *G. Kreil, G. Suchanek*, and *I. Kindås-Mügge*. According to feeding experiments with radioactive amino acids, bees produce in their venom glands promellitin, a precursor of the poison proper, which is about 8 or 9 amino acids longer at the N-terminus. The mRNA for mellitin has been isolated from the venom glands of young queen bees. After injection of this RNA into frog oocytes a polypeptide very similar to promellitin was synthesized; translation in cell-free mammals or plants on the other hand led to prepromellitin, which, in contrast to promellitin, contains further amino acid residues at the N and C terminus. [Biosynthesis of a Secretory Peptide in Honey Bee Venom Glands: Intermediates Detected *in vivo* and *in vitro*. Fed. Proc. *36*, 2081—2086 (1977); 45 references]

[Rd 994 IE]

Short-term effects of hormones on the carbohydrate and lipid metabolism of the liver are described in an article by *D. A. Hems*. A series of hormones, mostly peptides, influence the catabolism of liver glycogens and fats. Not all of them act *via* cyclic nucleoside phosphates; probably the Ca^{2+} level plays a role in some cases. Elucidation of the mode of action could contribute to a better understanding of the reaction of the cell membrane of the regulation processes, and perhaps also endocrine disturbances. [Short-term Hormonal Control of Hepatic Carbohydrate and Lipid Catabolism. FEBS Lett. *80*, 237—245 (1977); 60 references]

[Rd 995 IE]

N—C=C—C=O compounds ("enaminones") of type *(1)* are described in an article by *J. V. Greenhill*. These vinylogous amides or vinylogous urethanes are mainly used for the synthesis of heterocycles, *e.g. (2)* and *(3)*. Enaminones, which



can be regarded as protected amines, are possibly also potential precursors for drugs. [Enaminones. Chem. Soc. Rev. *6*, 277—294 (1977); 61 references]

[Rd 996 IE]

Reactions of organosulfur compounds promoted by metal ions are reviewed by *D. P. N. Satchell*. A typical example is the hydrolysis of thiol esters in aqueous solvents. This spontaneous reaction is catalyzed by H^+ (weakly) [eq. (1)], and by Hg^{2+} or Ag^+ (strongly) [eq. (2)]. The reactions of thiols, disulfides,

$$RCO{-}SR' + H_2O \xrightarrow{H_3O^+} RCO_2H + R'SH \quad (1)$$

$$RCO{-}SR' + 2H_2O + Ag^+ \rightarrow RCO_2H + R'SAg + H_3O^+ \quad (2)$$

thioethers, thioacetals, thioesters, thioacids, thioanhydrides, and thioamides are described. In these compounds sulfur is divalent and can interact directly with the metal. Apart from Hg and Ag, *inter alia*, Pb, Cd, Pt, Pd, Ni, Fe, Cu, Au, and Tl in the form of their ions are also suitable for these reactions. [Metal-ion-promoted Reactions of Organo-sulphur Compounds. Chem. Soc. Rev. *6*, 345—371 (1971); 65 references]

[Rd 997 IE]

The Analytical Chemistry of Synthetic Dyes. Edited by *K. Venkataraman*. John Wiley & Sons, New York—London 1977. xxiv, 591 pp., numerous figs. and tables, bound, £ 31.90.

This book, a collaborative effort of 23 authors, presents in 20 chapters the method used in dyestuff analysis. The physicochemical methods customarily used in the analysis of dyestuffs are treated in the first ten chapters (thin-layer chromatography, paper chromatography, paper electrophoresis, high-pressure liquid chromatography, gas chromatography, colorimetry in dyestuff solutions, IR, NMR, and mass spectrometry, as well as X-ray diffraction), though in these descriptions fundamental theoretical and practical knowledge is assumed. The standpoint of methodical application to dyestuff analysis is given prominence, and the articles therefore correspond to the readers' expectations. Somewhat too little information is given in the chapter on mass spectrometry: having 13 pages, it is about the same length as the chapter on gas chromatography (11 pages), which is relatively unimportant for dyestuff analysis.

The chapter on methods of chemical degradation is too short, and in addition the references given are sometimes difficultly accessible. Some procedures, *e.g.* pyrolysis and dry distillation with alkali metal hydroxides, are described too briefly, although in difficult cases these can provide decisive evidence for the structure of a dye.

The identification of dyes and pigments on their substrates is treated well and extensively. A chapter on quantitative dyestuff analysis deals mainly with dyes fixed on textile fibers. Special themes, such as analysis of hair dyes and of dyes for foods, drugs, and cosmetics, are also treated. The conclusion of the book is an opportune contribution to ecological and toxicological problems.

By and large, *Venkataraman*'s new book provides a satisfactory presentation of the themes discussed. The 1200 references help in delving deeper into specific questions. The book closes a gap in the chemical literature; it will be welcomed not only by the dyestuff analyst but will also prove of value to the dyestuff chemist engaged in preparative work.

Dietmar Augart [NB 385 IE]

Energetic Materials. Vol. 1. Physics and Chemistry of the Inorganic Azides. Edited by *H. D. Fair* and *R. F. Walker*. Plenum Press, New York 1977. 1st edit., xv, 503 pp., numerous figs. and tables, bound, $ 59.40.

Although azides have been known since 1890 and a large number of ionic and covalent inorganic azides have been prepared, most of the detailed work on their physical properties in particular was done only in the last two decades.

The present book opens with a brief introduction followed by nine main chapters to which several authors contributed. These deal mainly with the physical properties of azides and with their decomposition reactions induced by physical means, the literature up to about 1975 being considered. The first chapter gives a review of the inorganic and organometallic azides and of the general and special methods used in their preparation. Next information is provided about crystal growth and crystal structures, very many data being presented in tables and important structures being illustrated. There is an excellent and very extensive review of molecular and lattice vibrations, of optical and electrical properties, and of electron structure calculations. The last four chapters deal very carefully with the stability of azides and with their slow or rapid decomposition induced by heat, friction, impact, electricity, or irradiation. The progressive development of explosions is demonstrated by many photographs.

For all who work with azides this book can be strongly recommended as a mine of information on the literature and data available on the physicochemical behavior of this class of compounds. The data are presented critically and from diverse points of view, and open questions are faced honestly and not simply buried.

Armin Schmidt [NB 388 IE]

Energetic Materials. Vol. 2. Technology of the Inorganic Azides. Edited by *H. D. Fair* and *R. F. Walker*, Plenum Press, New York 1977. 1st edit., xiv, 296 pp., numerous figs. and tables, bound, $ 47.40.

The information collected in the last twenty years on the technology of azides, in particular the technology of lead and silver azides, is reported in this book in a set of seven chapters.

The first chapter contains a really detailed account of the preparation, stabilization, and processing of lead and silver azides. The plant used for their manufacture and the products are illustrated by photographs. Many physical properties of the products stabilized in a variety of ways are tabulated. A further chapter deals with the analysis of, in particular, industrial products for their azide content and traces of metals. In line with the character of these compounds, the following four chapters are devoted in particular detail to the handling, storage, and destruction of these materials, to sensitivity tests, and to their reactions and to impact, friction, heat, radiation, and electricity. The physiological action of azides is also mentioned. The last chapter concerns the use of azides as detonators and as explosives.

The book as a whole contains an abundance of industrially important data, plant, and technical drawings. If we except the analytical chapter, the book will thus be of the greatest value to readers with industrial interests. On the other hand, it would be advantageous to all dealing with azides to learn the many tests that permit statements to be made about the behavior of this class of compounds toward external influences.

Armin Schmidt [NB 389 IE]

Grundlagen der enzymatischen Analyse (Principles of Enzymatic Analysis). Edited by *H. U. Bergmeyer* in collaboration with *K. Gawehn*. Verlag Chemie GmbH, Weinheim—New York 1977. 1st edit., xii, 267 pp., 99 figs., 30 tables, bound, DM 44.—.

The many new procedures of enzymatic analysis and the increasing mechanization of modern clinical and biochemical laboratories led to the decision to publish separately the chapter on "Principles of Enzymatic Analysis" from *Bergmeyer*'s valued major work[*].

The book is divided into the following main sections: 1. Introduction, 2. Theoretical Principles, 3. Handling of Biochemical Reagents and Sample Material, 4. Techniques of Measurement and Apparatus, and 5. Obtaining and Assessing Results of Measurements.

Naturally, for methods for the determination of individual enzymes, the reader must still turn to the larger work. The "Principles" rather explain the quantitative procedures customary today and the experimental details of biochemical analysis. The conclusion is a review of the numbering and

[*] Cf. Angew. Chem. Int. Ed. Engl. *14*, 268 (1975).

classification of enzymes, the new SI units, and a table of numerical values and their units. The book can thus be recommended not only as an aid to students but also as an introduction to all research groups and experimental workers in biochemistry and clinical chemistry.

Joachim Jentsch [NB 395 IE]

Gaschromatographie (taschentext 48) (Gas Chromatography) (Pocketbook 48). By *G. Schomburg*. Verlag Chemie GmbH, Weinheim—New York 1977. 1st edit., x, 188 pp., 62 figs., 7 tables, br., DM 22.—.

Although the importance of gas chromatography as a method of separation is increasing steadily in research and industrial applications, there is hardly any new introductory monograph that is in any way adequate for the present state of development in this field. The book now under review undoubtedly fills a gap in the market in that, being written for the newcomer to gas chromatography, it emphasizes above all the practical aspects and steers him away from typical mistakes. The chapter on modern GLC equipment is restricted to the essentials without forgetting important new techniques. It is useful to have the comparative description of the commercially available instruments from the experienced experimentalist's point of view. Particular care is given to working out the possibilities of systematizing the qualitative and quantitative results in respect of "reproducibility, comparability, and accuracy". This chapter is supplemented in the experimental part of the book by some fundamental exercises with exact experimental data. The theoretical principles of gas chromatography, the parameters important for the experimental worker, and the consequences of their variation in operation of a GLC system are presented clearly and intelligibly. Only the experts will note that *Schomburg* entirely avoids use of the customary term "Trennzahl" [separation number] and limits the somewhat controversial concept of separation performance to "Trennstufenzahl" [number of separation stages] and "Auflösung" [resolution].

The book is so very suitable for helping the beginner to gas chromatography over the initial difficulties that it should be highly welcome to Technical College teachers as a basis for tuition in this subject.

W. A. König [NB 396 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Lithium Aluminium Hydride. By *J. S. Pizey*. From the series "Synthetic Reagents". Edited by *J. Pizey*. Ellis Horwood, Chichester/John Wiley & Sons, New York 1977. 234 pp., bound, £ 9.00.—ISBN 85312-081-1

Hochdruck-Flüssigkeits-Chromatographie. By *H. Engelhardt*. Vol. 14 of "Anleitungen für die chemische Laboratoriumspraxis". Edited by *F. L. Boschke, V. A. Fassel, W. Fresenius, J. F. K. Huber, E. Pungor, W. Simon*, and *T. S. West*. Springer-Verlag, Berlin 1977. 2nd, revised and enlarged edition, xii, 257 pp., bound, DM 64.—.—ISBN 3-540-08263-8

Supraleitung. Grundlagen und Anwendungen. By *W. Buckel*. Physik Verlag, Weinheim 1977. 2nd revised and enlarged edition, xv, 325 pp., paperback, DM 42.—.—ISBN 3-87664-031-8

Isotopic Studies of Heterogeneous Catalysis. By *A. Ozaki*. Kodansha, Tokio/Academic Press, New York 1977. viii, 239 pp., bound, $ 25.00.—ISBN 0-12-531950-9

Polymer Rheology. By *L. E. Nielsen*. Marcel Dekker, New York 1977. ix, 203 pp., bound, SFrs. 58.—.—ISBN 0-8247-6657-1

Coal Desulfurization. By *R. A. Meyers*. Marcel Dekker, New York 1977. xii, 254 pp., bound, SFrs. 98.—.—ISBN 0-8247-6572-9

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Nitrogen as Leaving Group: Dediazoniations of Aromatic Diazonium Ions

By Heinrich Zollinger[*]

On heating, aromatic diazonium salts eliminate nitrogen by two fundamentally different mechanistic pathways, *i.e.* heterolysis and homolysis. Among these pathways a series of variants are known, giving rise to a whole variety of mechanisms. This article considers the effect of specific solvation, apparently characteristic of diazonium ions, by various solvents (fluorinated alcohols, methanol, water, dimethyl sulfoxide, pyridine, and hexamethylphosphoric triamide) on the mechanism. Apart from the donor properties of the solvent, the oxidation potential and the presence of additives play a major role in determining what reaction type will predominate.

1. Introduction

Molecular nitrogen is one of the best nucleofugic leaving groups known: diazoalkanes afford carbenes *via* metastable diazonium ions; in aromatic diazonium ions nitrogen is readily replaced by nucleophiles, especially by solvent. A comprehensive account of nitrogen as leaving group in aliphatic diazonium ions has been written by *Kirmse*[1]. Several years ago we reported[2] the current state of knowledge about the mechanisms of aromatic dediazoniations and expressed the belief that a number of open questions would soon be answered. This has indeed come about: in this connection a reaction was discovered which would hardly have been deemed possible in 1973, *i.e.* the reaction of molecular nitrogen with intermediates of aromatic dediazoniation[3]. The time is therefore ripe for a survey of known mechanisms of decomposition of aromatic diazonium ions.

In the following we shall adopt the systematic nomenclature of substitution reactions proposed by *Bunnett*[4]: regardless of mechanism, all reactions in which both nitrogen atoms of an azo or diazo compound are replaced by another group are designated dediazoniations; this term is preceded by the name of the entering group. A Gomberg-Bachmann arylation is accordingly designated as aryl-dediazoniation, a hydrolysis as hydroxy-dediazoniation, and replacement of the diazo group by hydrogen as hydro-dediazoniation.

This article is not a comprehensive compilation and discussion of all recent publications about the dediazoniations of aromatic diazonium salts. Instead, the main emphasis is placed on recent mechanistic findings relating to the heterolytic and homolytic thermal dediazoniations which have been obtained in solvents exerting a characteristic influence on the mechanism. These are 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide (HMPA), methanol, pyridine, and weakly alkaline aqueous buffer solutions. We shall not consider photodediazoniations.

As will become evident in the following sections, a *variety* of mechanisms has been found in the dediazoniations of aromatic diazonium salts. This is surprising, since only an S_N1-type dissociation of the diazonium ion to an aryl cation and N_2 would be expected by analogy with the dediazoniation step of aliphatic diazonium ions and from the extremely high stability of the nitrogen molecule.

However, two characteristic examples should suffice to show that seemingly slight modifications in the reaction system can lead to entirely different reaction products; these suggest fundamentally different dediazoniation mechanisms:

1) As already observed by *Horner* and *Stöhr*[5] and by *DeTar et al.*[6], and thoroughly investigated by *Bunnett et al.*[7], numerous arene diazonium ions in methanol decompose in a nitrogen atmosphere with formation of the corresponding

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hydrocarbon, *i.e.* a hydro-dediazoniation occurs (a); in the presence of oxygen, however, methoxy-dediazoniation (b) takes place.

$$Ar{-}N_2^{\oplus} + CH_3OH \begin{cases} \xrightarrow[N_2]{\text{under}} Ar{-}H + CH_2O + H^{\oplus} + N_2 & \text{(a)} \\ \xrightarrow[O_2]{\text{under}} Ar{-}OCH_3 + H^{\oplus} + N_2 & \text{(b)} \end{cases}$$

2) In DMSO as solvent, aryl-dediazoniation of the unsubstituted benzenediazonium ion with nitrobenzene leads mainly *via meta* substitution to 3-nitrobiphenyl, whereas in the case of the *p*-nitrobenzenediazonium ion the formation of *ortho*- and *para*-substituted products (2,4'- and 4,4'-dinitrobiphenyl) prevails[8]. This indicates an electrophilic aromatic substitution in the former case, and a radical mechanism in the latter case.

2. Dediazoniations in Trifluoroethanol and in Hexafluoroisopropanol

On the basis of the classical studies by *Crossley et al.*[9] dating from 1940, it was long accepted without question that the hydrolysis of arenediazonium salts in acid solution proceeds by an S_N1 mechanism, *i.e.* consists of a rate-determining irreversible dissociation of the diazonium ion into an aryl cation and nitrogen and fast subsequent reaction of the cation with water or other nucleophiles present in solution [eqs. (c) to (e)]. Apart from a somewhat neglected publication by *E. S. Lewis* and *Hinds*[10] in 1952, the first doubts regarding the correctness of this concept were voiced in 1964 when reactions were discovered whose kinetics could be influenced by the concentration of nucleophiles present in the system[11-13].

$$Ar{-}N_2^{\oplus} \xrightarrow{\text{slow}} Ar^{\oplus} + N_2 \qquad \text{(c)}$$

$$Ar^{\oplus} + H_2O \xrightarrow{\text{fast}} Ar{-}\overset{\oplus}{O}H_2 \xrightleftharpoons{\text{fast}} ArOH + H^{\oplus} \qquad \text{(d)}$$

$$Ar^{\oplus} + Nu^{n\ominus} \rightarrow Ar{-}Nu^{(n-1)\ominus} \qquad \text{(e)}$$

Nu = nucleophile, $n = 0, 1, 2$, *etc.*

The question whether aryl cations are indeed intermediates of heterolytic dediazoniations therefore still remained to be answered[2] in 1973.

Not long afterwards a solution to the problem came from two quarters: *Swain et al.*[14,15] investigated and interpreted the effects of substitutions on the kinetics of dediazoniation in water: the kinetic results were analyzed by use of dual parameter substituent constants $\mathcal{F}$ (=field effect) and $\mathcal{R}$ (resonance effect) and, according to *Swain* and *Lupton*[16], are compatible with the intermediacy of an aryl cation but not with an S_N2-type transition state. The same conclusion was reached by *Swain et al.*[14,17] from the primary kinetic isotope effects in the dediazoniation of ^{15}N-labeled arenediazonium ions and the secondary kinetic isotope effects in the dediazoniation of ring-deuterated salts.

The occasional influence of nucleophile concentration on the reaction rate could not be interpreted in this way; it can, however, be understood from the observation that the formation of aryl cation and N_2 is reservible: in our laboratory it was shown by ^{15}N-labeling experiments that aryl cations generated from ^{15}N-diazonium ions are able to form ^{14}N-diazonium ions with "external" $^{14}N_2$ molecules[3,18], *i.e.* that the reverse reaction of eq. (c) is possible [see eqs. (f) and (g)]. Hence the aryl cation is a steady-state intermediate which, according to classical Bodenstein kinetics [eq. (h)], must lead to a drop in the overall reaction rate on increasing the concentration of nitrogen and to a rise in the rate on increasing the concentration of the nucleophiles.

$$Ar{-}N_2^{\oplus} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ar^{\oplus} + N_2 \qquad \text{(f)}$$

$$Ar^{\oplus} + Nu^{n\ominus} \xrightarrow{k_2} Ar{-}Nu^{(n-1)\ominus} \qquad \text{(g)}$$

$$v = [Ar{-}N_2^{\oplus}] \frac{k_1 k_2 [Nu^{n\ominus}]}{k_{-1}[N_2] + k_2[Nu^{n\ominus}]} \qquad \text{(h)}$$

This could indeed be confirmed in 2,2,2-trifluoroethanol (TFE) and in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[19]: radical side reactions are exceptional in these very weakly nucleophilic solvents, in contrast to the situation in water. The kinetic effects are larger owing to the greater solubility of nitrogen.

Furthermore, it was found that the N_α-N_β rearrangement, *i.e.* the reaction

$$Ar{-}\overset{\oplus}{N}_\alpha{\equiv}{}^{15}N_\beta \rightleftarrows Ar{-}{}^{15}\overset{\oplus}{N}_\alpha{\equiv}N_\beta$$

occurs to a greater extent in TFE and HFIP than in water. This rearrangement was first observed in water (1–2% after 70% dediazoniation) by *E. S. Lewis*[20], but was suspected to be a mere artifact[21]. With the 2,4,6-trimethylbenzenediazonium ion ($^{15}N_\beta$) the extent of N_α-N_β rearrangement after 70% dediazoniation reaches 20.9 and 37.0% in TFE and HFIP, respectively[19].

In TFE the aryl cation could also be trapped by carbon monoxide, which is isoelectronic with molecular nitrogen[18]

$$Ar^{\oplus} + CO \rightarrow Ar{-}\overset{\oplus}{C}{=}O \rightarrow \rightarrow Ar{-}CO{-}OCH_2CF_3$$

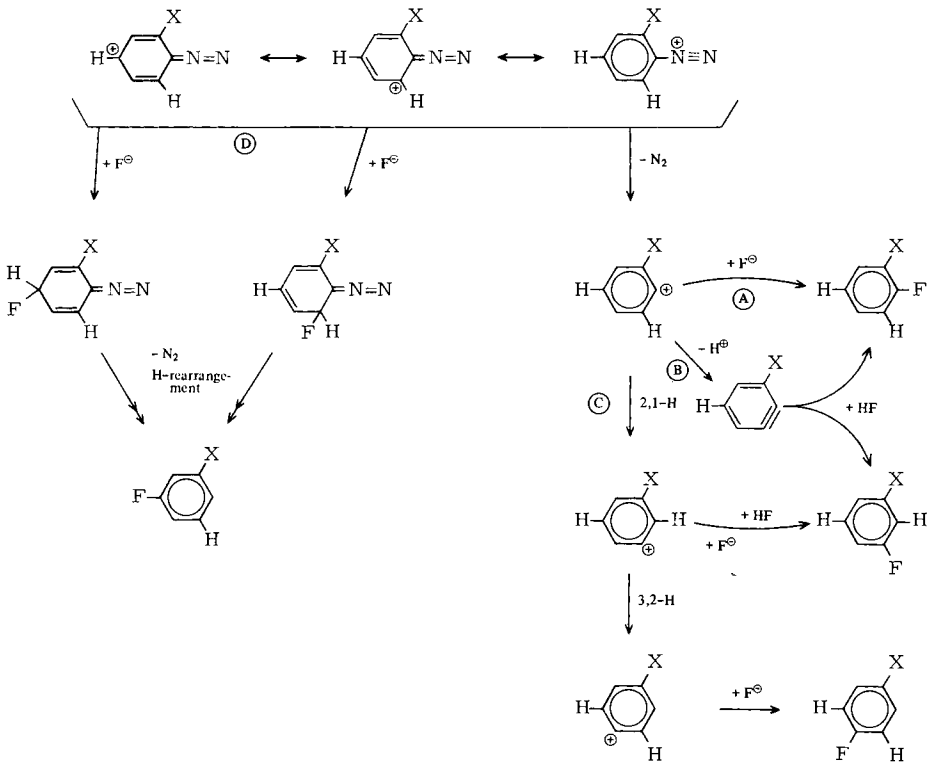
This reaction was unsuccessful when attempted in water by *Lewis et al.*[10].

Becker, Kuzmin, et al.[22] have interpreted the short-lived intermediates detected by flash photolysis of aqueous solutions of diazonium salts as aryl cations. Supporting evidence for this assignment comes from the substituent dependence of the rate of hydrolysis of these intermediates, which obeys the classical Hammett relation with a predictably small ϱ value (+0.36) owing to the high reactivity. In the light of a recent study[23], however, it appears doubtful that these intermediates are aryl cations.

Dediazoniation *via* aryne intermediates, known to be possible in some cases[24], could be ruled out experimentally by *Swain et al.*[15] and by our own group[13] for the reaction conditions under discussion.

The products of dediazoniation in pyridinium polyhydrogenfluoride investigated by *Olah et al.*[25] clearly demonstrate the versatility of heterolytic dediazoniations. The product ratio suggests that, apart from S_N1 substitutions and reactions *via* arynes, σ-substitutions of the type described by *Kovacic*[26]

and S_N1 substitutions with 2,1- and 3,2-hydrogen shifts may also occur (Scheme 1).



Scheme 1. Dediazoniation in pyridinium polyhydrogenfluoride solution. X = CH_3, path Ⓐ; X = NO_2, path Ⓓ; X = CF_3, paths Ⓑ + Ⓒ + Ⓓ.

Let us now concentrate on path Ⓐ, and particularly on the question whether the path (f)→(g), *i.e.* the mechanism involving *one* steady-state intermediate, the aryl cation, provides the only possible interpretation of the experimental data.

To this end it seems logical to examine whether the kinetic data for dediazoniation of 2,4,6-trimethylbenzenediazonium ion in TFE and HFIP are compatible with the dependence on nitrogen concentration $[N_2]$ expected from eq. (h). $[N_2]$ can be increased in this solvent by working at a higher nitrogen pressure. Figure 1 shows the results of kinetic measurements at 1–300 atm of argon or nitrogen: the drop in rate expected from eq. (h) at increased nitrogen pressure, *i.e.* increased nitrogen concentration, is clearly observed—however, it also occurs, although to a lesser extent, with argon! The reason for this effect of argon pressure on the rate (argon can be assumed not to react with aryl cations) is to be found in the known[27] activation volume of dediazoniation. The effect can be eliminated by performing kinetic experiments at constant total pressure (300 atm) with argon/nitrogen mixtures and determining the solubility of nitrogen in TFE under these conditions by a direct method[19]. The solubility of nitrogen in TFE is found to be about 23 times higher than in water. This is another reason why TFE is an ideal solvent for the study of heterolytic dediazoniations!

Kinetic measurements under pressures of 300 atm are not simple: statistical evaluation of 41 runs gave a standard deviation of $\pm 0.5\%$ to $\pm 2.8\%$ for the first order rate constant. The 41 experimental k_{exp} values measured at eight different nitrogen concentrations between 0 and 3.053 mol/l were shown by F tests to be compatible not only with the function (k), which corresponds to the kinetic equation (h) for the "simple" aryl cation mechanism, but also—although not so well—with a linear dependence of the rate constant k_{exp} on $[N_2]$; *i.e.* with function (i) or—more satisfactorily—with function (l)[28].

$$k_{exp} = a - b[N_2] \quad \text{(i)}$$

$$k_{exp} = \frac{a'}{b'[N_2] + c'} \quad \text{(k)}$$

$$k_{exp} = \frac{a''}{b''[N_2] + c''} + d'' \quad \text{(l)}$$

Eq. (i) can be ruled out mechanistically: this function would correspond (under certain boundary conditions) to a *com-*

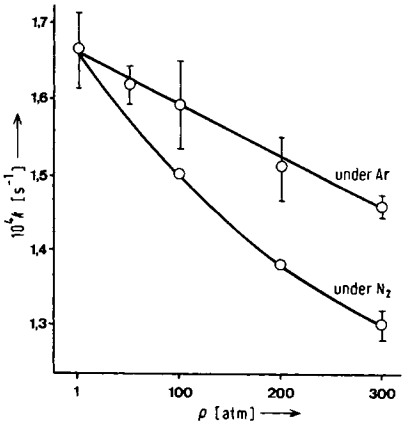


Fig. 1. Rate of dediazoniation of 2,4,6-trimethylbenzenediazonium tetrafluoroborate in TFE at increasing nitrogen and argon pressures [19].

pletely reversible reaction. It is impossible, however, to regenerate the diazonium salt from the *final* products of dediazoniation and nitrogen.

The function (l) can be ascribed to several mechanistic variants with *two* steady-state intermediates. These intermediates may occur competitively or consecutively[28].

Let us note that it is concluded all too frequently and far too hastily from kinetic data that any mechanism compatible with experimental work is the right one. This conclusion is *fundamentally* false[29]. It is only correct to say that a mechanism which fits the data cannot be discounted; other mechanisms may also be compatible with the experimental data. Perhaps the first mechanism can be ruled out by *further* experiments.

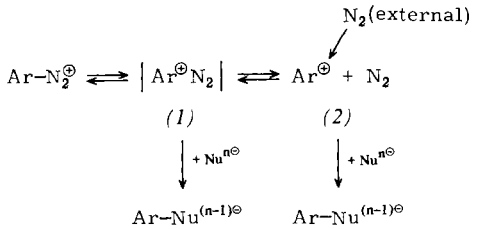
Dediazoniation mechanisms with two competitive or consecutive intermediates have already been proposed by *Lewis et al.*[11] for the reaction of diazonium salts with thiocyanate ions; a decision has yet to be made.

In our case, differentiation of the functions (k) and (l) became possible by use of special statistical methods. Function (k) can be ruled out within the probability limits set by the accuracy of the kinetic measurements.

Evidence supporting (l), *i.e. two* (or more) steady state intermediates, also comes from purely chemical criteria:

N_α-N_β rearrangement proceeds much faster than the reaction with external nitrogen. Thus after 70% conversion of 2,4,6-trimethylbenzenediazonium tetrafluoroborate (in HFIP, $[N_2]=4.94$ mol/l), N_α-N_β rearrangement could be detected, as already mentioned, in 37.0% of the remaining diazonium salt, whereas exchange with external nitrogen had occurred in only 16.5% of the salt. Moreover, steric substituent effects (comparison of benzene- with 2,4,6-trimethylbenzenediazonium salts) and solvent effects (comparison between HFIP and TFE) on the kinetics of exchange and N_α-N_β rearrangement can hardly be explained without assuming two or more intermediates.

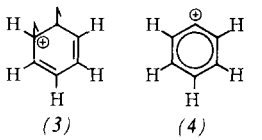
These results are compatible with the conclusion that the N_α-N_β rearrangement takes place in an initial intermediate, possibly corresponding to the encounter complex[30] but that exchange with external nitrogen requires a "free" aryl cation.



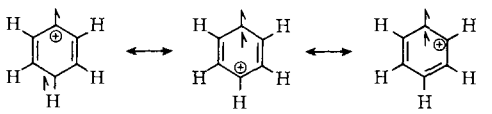
The initial intermediate *(1)* corresponds to a contact ion pair, as first proposed by *Winstein et al.* for the generation of carbocations from molecules[31]. Species *(1)* should therefore be described as a contact ion-molecule pair[32]. In contrast to *Winstein*'s ion pairs, coulombic interaction does not contribute to the stability of the pair $|Ar^{\oplus}N_2|$. The relative stability of *(1)* can be understood *qualitatively* in terms of orbital interaction diagrams, as have been considered for addition of a proton to a C=C double bond[33], and with the aid of HOMO/LUMO concepts[34].

Distinction between the reactivity of encounter complex-type intermediates such as *(1)* and that of solvent-separated and "free" aryl cations (or ion pairs) such as *(2)* could be a problem of selectivity disguised by microdiffusion, as studied by *Rys*[35].

A further question still to be answered is the structure of the aryl cation: in 1961 *Taft*[36] postulated that the aryl cation exists as a biradical *(3)*. However, recent *ab initio* MO calculations[37] show the singlet structure *(4)* to be more stable than a biradical *(3)* or triplet structure *(5)* for the unsubstituted phenyl cation. This result confirms earlier semi-empirical calculations[38].



(3) *(4)*



(5)

The biradical hypothesis was based on the effect of substituents on the kinetics of dediazoniation, which were not understood at the time. As already mentioned, this problem has meanwhile been solved by *Swain*[15]: a biradical can be ruled out.

Evidence favoring a triplet (of the ground state) is provided, however, by ESR spectra recorded at 77 K on photolysis of arenediazonium salts bearing electron donor substituents in the *para* position[39], and also by the influence of diluent on the stereospecificity of addition of *cis*-2-butene to 2,6-di-*tert*-butyl-4-diazo-2,5-cyclohexadienone ("3,5-di-*tert*-butylbenzene 1,4-diazoxide")[40]. *Ab initio* calculations on the stability of arenediazonium ions with donors in the *para* position (NH_2, OH) are also compatible with a triplet[41].

Remarkably, with the exception of a conjecture concerning the intermediate in the case of the *p*-nitro compound[42], these demonstrations of triplet character are limited to aryl cations having electron donors in the *para* position. Generalization of this result seems unjustified for the following reasons: it is quite possible that singlet or triplet structures may be preferred depending upon the substitution of the benzene ring and there is consequently the possibility of two (competitive or consecutive) intermediates at some stage of the association process (such as ion-molecule pairs and ion pairs).

The significance of a detailed examination of aryl cation-type intermediates of heterolytic dediazoniation far exceeds this particular reaction because it has so far proved impossible to demonstrate the occurrence of aryl cations in other reactions. Only recently, four research teams jointly reported unsuccessful attempts to produce aryl cations from activated arenesulfonates (*e.g.* from trifluoromethanesulfonates) by analogy with the known vinyl cations[42a].

3. Dediazoniation in Dimethyl Sulfoxide

On account of the isomeric ratios already mentioned for arylation with *p*-nitrobenzenediazonium salts in dimethyl sulf-

Table 1. Dediazoniation products of *p*-nitrobenzenediazonium tetrafluoroborate in DMSO at 50°C in the absence or presence of iodobenzene (Ar = *p*-O_2N—C_6H_4) [43].

Experimental group	ArN_2BF_4 [mol/l]	C_6H_5I [mol/l]	Yield [%] Ar—OH	Ar—H	Ar—F	Ar—$SOCH_3$	Ar—CH_2SOCH_3	Ar—SCH_3	Ar—I
1	2×10^{-2}	—	88–90	1–2	<0.1	<0.1	<0.1	trace	—
2	2×10^{-2}	2×10^{-2}	16–18	4–5	*	*	*	*	1–2
3	8×10^{-2}	8×10^{-2}	16–27	8	*	*	*	*	6–14

*: Not determined.

oxide (DMSO), it appeared of interest to study the decomposition of these salts in DMSO in the absence of aromatic substrates[43]. Group 1 in Table 1 shows that *p*-nitrophenol is formed in high yield. If the reaction is performed in ^{18}O-DMSO, the oxygen of the phenolic OH group is found to arise exclusively from DMSO. In the presence of iodobenzene (experimental groups 2 and 3) the yield of *p*-nitrophenol falls off sharply; nitrobenzene (from hydro-dediazoniation) is accompanied by 1-iodo-4-nitrobenzene and also by a large amount of unidentified polymeric material. All these products, and especially ArI formed by iodine transfer according to *Bunnett, Cadogan, et al.*[44], are unmistakable indications of a radical decomposition. Up to 90% conversion, the reaction strictly obeys 1st order kinetics. That is rather unusual for radical dediazoniation. The reaction rate is constant within the limits of experimental error, whether the reaction is performed under nitrogen, under air, in glass or Teflon vessels, or even in a mixture of DMSO and benzene (2:1) and in the presence of an equivalent of iodobenzene, although different products are formed under the two last-mentioned sets of conditions. The reaction proceeds about ten times faster than in acidic aqueous solution where it follows a heterolytic course.

It is also remarkable that the electronic spectrum of this diazonium salt in DMSO differs significantly from that recorded in water or TFE, and that admixture of benzene up to a ratio DMSO:benzene of 1:2 hardly alters the spectrum typical for pure DMSO solution.

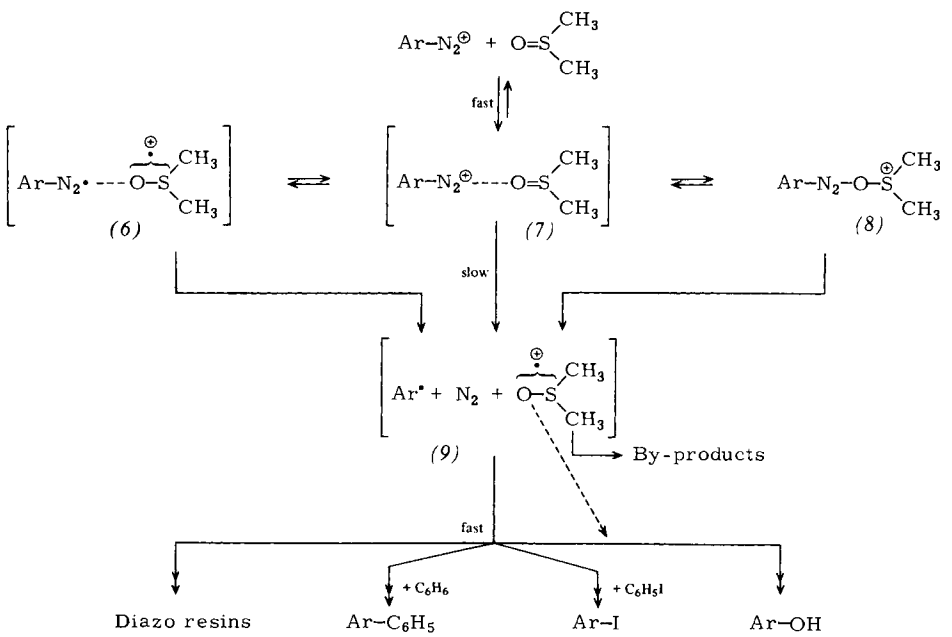
All these results are compatible with the reaction mechanism shown in Scheme 2.

The UV spectra suggest that equilibrium between the diazonium ion and the solvent, on the one hand, and the electron donor-acceptor complex *(7)* (charge-transfer complex), on the other, lies on the side of the complex *(7)*. According to *Gutmann*[45], DMSO is a good electron donor solvent. This complex might possibly not exist in the form of *(7)* but as a radical pair *(6)* or covalent compound *(8)*. Dissociation of this complex in a cage *(9)* to form an aryl radical, a nitrogen molecule, and the radical cation corresponding to DMSO is slow and rate-determining. Fast subsequent steps lead to the products obtained.

The observation that addition of pyridine enhances the rate of decomposition, shifts the order of reaction from unity to zero, and considerably diminishes formation of *p*-nitrophenol also warrants attention. This is compatible with superior electron donor properties of pyridine as compared to DMSO[45]: generation of the corresponding diazopyridinium cation in one or several of the forms corresponding to *(7)*, *(6)*, and *(8)* competes with formation of *(7)*. This observation plays an important role in the discussion in Section 7.

4. Dediazoniation in Hexamethylphosphoric Triamide

Numerous methods have been reported for the reduction of diazonium salts, *i.e.* for replacement of the diazonio group by hydrogen (hydro-dediazoniation, eq. (a)). The most recent literature survey has been completed by *Tröndlin* and *Rüchardt*[46]. We shall consider just one system in detail



Scheme 2

because it is of importance for the solvation effects discussed in Section 7, *i.e.* hydro-dediazoniation in hexamethylphosphoric triamide (HMPA). This reaction was discovered by *Newman et al.*[47] and examined mechanistically by *Tröndlin* and *Rüchardt*[46].

This dediazoniation is significantly faster than the reaction in DMSO. Determination and evaluation of the order of reaction according to time and concentration (n_t and n_c, respectively) with respect to diazonium salt and HMPA (in HMPA/acetonitrile mixtures) and the effects of inhibitors and initiators are compatible with a chain mechanism. The IR spectrum strongly suggests occurrence of the immonium salt *(10)*.

$$Ar\bullet + H_3C{-}\underset{\displaystyle CH_3}{N}{-}PO[N(CH_3)_2]_2 \longrightarrow Ar{-}H + H_2\dot{C}{-}\underset{\displaystyle CH_3}{N}{-}PO[N(CH_3)_2]_2$$

$$Ar{-}N_2^{\oplus} + H_2\dot{C}{-}\underset{\displaystyle CH_3}{N}{-}PO[N(CH_3)_2]_2 \longrightarrow Ar{-}N_2\bullet + H_2C{=}\overset{\oplus}{\underset{\displaystyle CH_3}{N}}{-}PO[N(CH_3)_2]_2 \quad (10)$$

$$Ar{-}N_2\bullet \longrightarrow Ar\bullet + N_2$$

Measurements of redox potentials disfavor electron transfer from HMPA to the diazonium ion; a diazoanhydride intermediate (A—N_2—O—N_2—Ar) analogous to the Gomberg-Bachmann reaction in water/arene mixtures[48] can be ruled out

$$HMPA + Ar{-}N_2^{\oplus} \downarrow$$

$$[(CH_3)_2N]_3\overset{\oplus}{P}{-}O{-}N_2{-}Ar \longrightarrow Ar\bullet + [(CH_3)_2N]_3\overset{\oplus}{P}{-}O{-}N{=}N\bullet \quad (11)$$

$$H^{\oplus} + H_2\dot{C}{-}\underset{\displaystyle CH_3}{N}{-}PO[N(CH_3)_2]_2 \longleftarrow [(CH_3)_2N]_3P{-}O^{\oplus\bullet} + N_2$$

for kinetic reasons. The authors therefore suspect an initiation reaction *via* an adduct *(11)* to the nucleophilic center, *i.e.* the oxygen of HMPA.

5. Dediazoniations in Methanol

The behavior of diazonium salts dissolved in methanol is of particular interest owing to the influence of the atmosphere (containing or devoid of O_2). As mentioned in Section 1, methoxy-dediazoniation [eq. (b)] usually predominates in the presence of oxygen whereas hydro-dediazoniation generally predominates under nitrogen or argon [eq. (a)].

Two papers published by *Bunnett et al.*[51] in 1968 are of considerable importance, not only because of the mechanistic discussion but also for methodological reasons: they demonstrate how difficult it is to resolve the influences of the individual reactions when performing such competition studies under very similar conditions.

All experimental data (product analyses and kinetic results), obtained with rigorous exclusion of oxygen, are compatible with a radical chain mechanism [eqs. (m) to (o)] already postulated in principle by *DeTar*[6,49]. The aryldiazo radical (Ar—N=N•) was demonstrated to exist as an intermediate by *Closs et al.*[50]. The rate constant of its decomposition [eq. (o)] was estimated to be 10^7 to $10^9\ s^{-1}$[32].

$$Ar\bullet + CH_3OH \rightarrow Ar{-}H + \bullet CH_2OH \quad (m)$$

$$\bullet CH_2OH + Ar{-}N_2^{\oplus} \rightarrow Ar{-}N{=}N\bullet + CH_2\overset{\oplus}{O}H \quad (n)$$

$$Ar{-}N{=}N\bullet \rightarrow Ar\bullet + N_2 \quad (o)$$

This chain reaction appears reasonable since it would give $CH_2\overset{\oplus}{O}H$ from which two thermodynamically highly stable compounds, *i.e.* formaldehyde *(12)* and methoxymethanol *(13)*, can be formed by proton transfer to the solvent.

$$CH_2\overset{\oplus}{O}H + CH_3OH \rightarrow CH_2O + CH_3\overset{\oplus}{O}H_2 \quad (12)$$

$$CH_2O + CH_3OH \rightarrow CH_3OCH_2OH \quad (13)$$

A question remaining unanswered by *Bunnett*'s investigation is that of the chain-initiating reaction. It could be homolysis of the addition product *(14)* of the diazonium ion and the solvent or electron transfer from methanol to the diazonium ion [eq. (p)].

$$Ar{-}N_2^{\oplus} + CH_3OH \rightleftharpoons Ar{-}N_2{-}\overset{\oplus}{\underset{\displaystyle H}{O}}\!\!\diagup^{CH_3} \quad (14)$$

$$Ar{-}N_2{-}\overset{\oplus}{\underset{\displaystyle H}{O}}\!\!\diagup^{CH_3} \longrightarrow Ar{-}N_2\bullet + H\dot{\overset{\oplus}{O}}{-}CH_3$$

$$Ar{-}N_2^{\oplus} + CH_3OH \longrightarrow Ar{-}N_2\bullet + H\dot{\overset{\oplus}{O}}{-}CH_3 \quad (p)$$

Bunnett et al.[7,51] consider eq. (p) to be more likely. We shall return to the fundamental problem of distinguishing between these two possibilities of generating the aryldiazo radicals in Section 7. Significantly, hydro-dediazoniation strongly predominates in alkaline methanol, *i.e.* in the presence of $CH_3O^{\ominus}Na^{\oplus}$[7,51].

A series of product analyses for experiments in the presence of radical scavengers such as 2-methyl-2-nitrosopropane and iodobenzene clearly demonstrate the intermediacy of aryl radicals. It is also remarkable that the *homolytic* dediazoniation generally predominates with diazonium ions rendered more electrophilic by suitable substitution at the aryl group. However, the effects of substituents on the rate of the homolytic reaction could not be correlated with any substituent constants (according to *Hammett*, *Taft*, *Swain*, *etc.*).

In contrast, the kinetics of the heterolytic component of dediazoniation in methanol responded to the same substituent effects as in water; the influence could therefore be interpreted in terms of the Swain substituent constants $\mathcal{F}$ and $\mathcal{R}$ (S_N1-type dediazoniation mechanism, (f)→(g); see Section 2).

With weakly electrophilic arenediazonium ions, the heterolytic mechanism predominates even in the absence of oxygen;

with chlorinated or brominated arenediazonium salts this occurs only in the presence of oxygen. Thus oxygen rapidly terminates the radical chain in these cases. Radical decomposition nevertheless prevails under oxygen with the *p*-nitrobenzenediazonium ion.

6. Behavior of Weakly Alkaline Aqueous Solutions of Diazonium Salts

Water is by far the most important solvent for diazonium salts. In the presence of *ca.* 10^{-2} mol/l or more mineral acid, dediazoniation proceeds almost exclusively *via* a S_N1-type mechanism involving the aryl cation[14,15,17] (cf. Section 2). Strongly alkaline (pH > 12) solutions of diazonium salts are very stable because—as shown[53] by *Hantzsch* in classical physical organic studies in the "pre-Ingold-Hammett" era[52]—they rearrange *via cis*-("*syn*"-)diazotates to the *trans*-("*anti*")-diazotates. It has long been known that diazonium salts decompose with comparative ease in the weakly alkaline range[54]. In spite of the considerable importance of such solutions for preparative work surprisingly little has been published about these dediazoniations.

The reason is soon discovered on making a serious attempt to investigate such a system: on the one hand, numerous polymeric products (diazo-resins) that are difficult to identify are formed at pH values between 6 and 11, and on the other hand these preparative and kinetic experiments are not readily reproducible. The material of the reaction vessel, light, and the atmosphere influence the product formation and the rate and order of the reaction to an extent rarely encountered in organic chemistry.

The dediazoniation of *p*-chlorobenzenediazonium tetrafluoroborate in $HCO_3^{\ominus}/CO_3^{2\ominus}$ buffers can be cited as an example[55,56]: in the presence of less than 10 ppb of O_2 it obeys first order kinetics in glass vessels, but zeroth order kinetics in Teflon vessels; between 50 and 100 ppb of O_2 a fast initial reaction slackens off after about 15% conversion; autocatalysis is observed on exposure to air, but a first order reaction once again in 100% O_2.

We know of three studies in which, under carefully selected conditions, the rate of dediazoniation peaks at the pH value corresponding to the pK_m value of the diazonium-*cis*-diazotate equilibrium[57-59]. This two-step equilibrium (q) is recognized[60] as unusual in that K_1 is smaller than K_2; hence there is no pH region in which the middle equilibrium species, the *cis*-diazohydroxide, accumulates to any extent. The experimental value pK_m corresponds to $1/2\ (pK_1 + pK_2)$.

$$Ar{-}N_2^{\oplus} \underset{-OH^{\ominus}}{\overset{+OH^{\ominus}}{\rightleftharpoons}} cis{-}Ar{-}N_2{-}OH \underset{+H^{\oplus}}{\overset{-H^{\oplus}}{\rightleftharpoons}} cis{-}Ar{-}N_2O^{\ominus} \qquad (q)$$

K_1 K_2

At $pH = pK_m$, the *cis*-diazohydroxide is actually present in very low concentration (normally < 0.1% of the analytical concentration of diazo compound); at this pH, however, a maximum of the possible concentration of diazohydroxide (Fig. 2) occurs. This provides substance for the supposition that dediazoniation proceeds *via* the diazohydroxide since the rate maximum of this reaction lies at $pH = pK_m$.

Moreover the equilibrium (r) at the same pH value shows a concentration maximum for the diazoanhydride (Fig. 2).

$$Ar{-}N_2^{\oplus} + Ar{-}N_2{-}O^{\ominus} \rightleftarrows Ar{-}N_2{-}O{-}N_2{-}Ar \qquad (r)$$

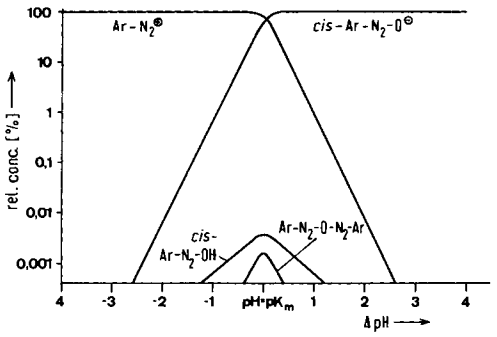


Fig. 2. Dependence of the relative concentration of the diazo equilibrium forms on the pH values (schematic) [56, 60].

The maximum of the dediazoniation at $pH = pK_m$ can therefore be explained just as well in terms of a mechanism involving the diazoanhydride. Such an interpretation would correspond to the results obtained by *Rüchardt et al.*[48] for the Gomberg-Bachmann reaction in water/arene mixtures.

A logarithmic plot of the percentages of diazoanhydride [eq. (r)] and diazohydroxide present at equilibrium [eq. (q)] *versus* the pH value has slopes of 2:1 and 1:1[56] (Fig. 2) on both sides of the maximum. This should provide an opportunity of distinguishing between diazoanhydride and diazohydroxide as dediazoniation intermediates on the basis of the slopes of the logarithmic reaction rates as plotted against the pH value. However, the slopes are different on each side of the rate maximum and have fractional values instead of 1:1 and 1:2.

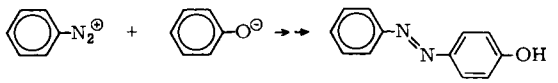
We shall have to await an accurate analysis before we know whether these fractional values are due to fractional reaction orders with respect to $[H^{\oplus}]$ and $[OH^{\ominus}]$ or to superposition of two or more mechanisms, each of which displays a different integral dependence upon the concentration of acid or base.

Fractional reaction orders with respect to the concentration of diazonium ion and/or other species suggest radical chain reactions. The occurrence of radical intermediates has been confirmed in various kinds of aqueous systems by ESR, CIDNP, kinetics, and product analyses. Since our survey[2] was published in 1973, numerous papers have appeared on this topic; only a few can be mentioned in the present discussion: apart from the dediazoniation in methanol considered in Section 5, a radical chain mechanism is compatible with the extremely thorough studies performed by *Rüchardt et al.*[61] on dediazoniation in aqueous solutions of $NaNO_2$ and with kinetic and spectroscopic measurements (including CIDNP) in mixtures of DMSO and pyridine[43] and of TFE and pyridine[62].

The problem of the initial step (cf. Section 5) could be solved for reaction in aqueous solution in the presence of nitrite ions[61] by invoking formation and radical decomposition of a *covalent* intermediate $Ar{-}N_2{-}NO_2$. This question remains to be answered in the case of adducts between diazonium ions and pyridine[62].

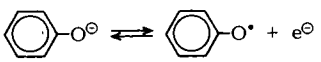
Experiments by *Becker et al.*[23,63] suggest that "free" electrons can be transferred from a donor to the diazonium ion: these authors observed that diazonium salts quench the fluorescence of pyrene (and other arenes) at a rate of $k_q = 2.5 \times 10^{10}$ mol l^{-1} s^{-1}. The pyrene radical cation and the arenediazo radical thus appear to be likely products of electron transfer. However, pyrene is a weak nucleophile; the concentration of its covalent product with the diazonium ion is estimated to lie below 0.01% at equilibrium. If electron transfer were to proceed *via* this potential intermediate present in such a low concentration then the measured rate constant could not be so large; however, dynamic fluorescence quenching in the excited state of the electron donor-acceptor complex preferred at equilibrium would fit the facts. Evidence supporting a diffusion-controlled electron transfer ($k = 1.8 \times 10^{10}$ to 2.5×10^{10} s^{-1}) was provided by pulse radiolysis.

The rate of heterolytic hydroxy-dediazoniation of type (f)→(d) is independent of pH in the pH range in which the diazo equilibria lie on the diazonium ion side (*i.e.* at pH < pK_m, cf. Fig. 2). Hence in weakly alkaline solution, the phenol corresponding to the diazonium ion is formed. At these pH values the phenol exists in equilibrium with the phenoxide ion and reacts readily with the diazonium ion to form the hydroxyazo compound *(15)*. The phenoxide ion has a redox

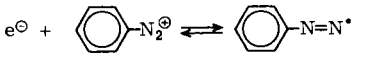


(15)

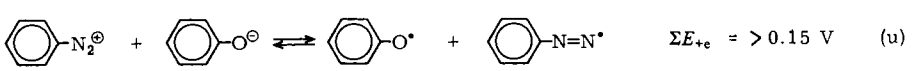
potential [eq. (s)] of the same order of magnitude as that estimated by *Waters*[64] for the diazonium ion⇄diazo radical equilibrium [eq. (t)]. Combination (u) of the two equations (s) and (t) reveals that formation of diazo radical and phenoxyl radical is favored in the optimum pH range (phenol-phenoxide equilibrium displaced towards phenoxide, diazo equilibria displaced towards the diazonium ion). *Bubnov et al.*[65] were able to detect radical intermediates in azo coupling of benzenediazonium salt and sodium phenoxide (in methanol) by means of ^{15}N-CIDNP.



E_{+e} = -0.45 V (s)



E_{+e} = > +0.6 V (t)



ΣE_{+e} = > 0.15 V (u)

Formation of phenol therefore *qualitatively* explains the complex kinetics of dediazoniation in weakly alkaline solution, in particular autocatalysis, the complex influence of oxygen (phenols undergo ready oxidative polymerization), and the formation of polymeric colored products containing considerable amounts of nitrogen.

7. Nucleophilic Solvation as a Mechanism-Determining Factor in Dediazoniations

Dediazoniations in a series of solvents have been described in Sections 2 to 6; these reactions exhibit a surprising and apparently inexplicable variety of mechanisms: there is not only *one* heterolytic and *one* homolytic decomposition pathway but several. Presumably, further mechanisms occur in other less thoroughly studied systems.

The observation[66] that methanediazonium ions are stable in the gas phase suggests that solvation plays an essential role in the dediazoniation of solutions of both aliphatic and aromatic diazonium ions.

The diazonium ion is an electrophilic reagent that is solvated in a special way insofar as *Ritchie*[67] failed to detect any reorganization of the solvation shell in the transition state of nucleophilic additions to the β-nitrogen (*e.g.* with $N_3^{\ominus}$, $CN^{\ominus}$, $OH^{\ominus}$).

It is not yet possible to define this "special kind of solvation" more precisely. However, in semiquantitative terms the concept of dual solvent parameters developed by *Gutmann*[45] can be applied to dediazoniations: solvents can behave as donors or as acceptors in the interactions with solutes. *Gutmann* recognized that these two properties can be determined independently with the aid of two suitable standard substrates and introduced two parameters, *i.e.* the donor number and the acceptor number (DN and AN, respectively). Depending upon the kind of solvation, one of the parameters can outweigh the other.

A similar approach was adopted earlier by *Koppel* and *Pal'm*[68] who sought to quantify the effect of the solvent by introducing four parameters which describe the nonspecific and the specific solvation as the result of the electrophilic and the nucleophilic properties of the medium. The latter were designated *E* and *B*.

On surveying the solvent systems considered in this article, it is seen that the ratio of heterolytic to homolytic reactions shifts in favor of formation of diazoaryl and aryl radicals along the series HFIP ≈ TFE < H_2O (acid) ≈ CH_3OH (acid) ≤ DMSO < HMPA; furthermore, radical formation in TFE, in water, and in DMSO is enhanced by pyridine. Nucleophilic additives such as phenoxide, $NO_2^{\ominus}$, and $OH^{\ominus}$ have a similar effect in water, as does methoxide in CH_3OH. This tendency to form radicals follows the series of *Gutmann*'s donor numbers (DN)[45], *Koppel* and *Pal'm*'s *B* values[68], and *Schleyer*'s N_{BS} nucleophilic indices[69] where they are known (Table 2).

Table 2. Solvent parameters.

Solvent	N_{BS} [69]	DN [45, 70]	B [68]	AN [45]
HFIP (97%)	−3.93	—	—	—
TFE (100%)	−2.78	—	—	—
H_2O	−0.26	*ca.* 30	123	54.8
CH_3OH	0.01	[a]	—	41.3
DMSO	—	29.8	193	19.3
Pyridine	—	33.1	220	14.2
HMPA	—	38.8	234	10.6

[a] The donor number for methanol is higher than 19.1, but lower than 33.8 [70].

Conversely, it could be deduced from the acceptor numbers (AN) of Table 2 that the lone pair of the β-diazo nitrogen acts as a donor in solvents having better acceptor properties, thus favoring heterolysis. However, since the rate of heterolytic dediazoniation is reported by *Swain et al.*[15,17], and also shown by our own kinetic measurements[28], to remain roughly constant in numerous solvents (aqueous sulfuric acid, glacial acetic acid, CH_2Cl_2, TFE, HFIP, fluorosulfuric acid), heterolysis seems much less susceptible to an acceptor effect than homolysis to a donor effect. A quantitative correlation between the donor number (according to *Gutmann*) and the rate of homolytic dediazoniation can hardly be expected because the donor numbers were measured for one particular system (acceptor properties of $SbCl_5$) and are therefore fundamentally incapable of accounting for specific effects which might be operative in the case of diazonium ions.

An insight into the kind of solvation of arenediazonium ions with DMSO is provided by the experiments cited in Section 3. Azo coupling experients in DMSO/H_2O mixtures[71] suggest that diazonium ions form more stable solvates with DMSO than with water.

It should be emphasized that this evidence only suggests that a specific nucleophilic solvation is necessary for homolytic dediazoniation; no information is forthcoming about the kind of interaction between the solvent molecule and the diazonium ion (covalent bonding, donor-acceptor complex, *etc.*).

This solvation is clearly essential for the actual electron transfer to the diazonium ion; however, it is not the only condition. The donor particle must also have a favorable redox potential, *i.e.* it must be capable of forming a relatively stable species on release of an electron. The nitrite ion, which is transformed into nitrogen dioxide, is an excellent example[61].

In this connection, *Becker et al.*[23] have compiled interesting correlations between oxidation potential of the donor and reduction potential of the diazonium ion. They were able to demonstrate that, of two fundamentally possible dediazoniation reactions, that reaction is favored in which the electron required for elimination of N_2 can be supplied with the lowest expenditure of energy. For the heterolytic reaction mode this will be "intramolecular" electron transfer from the aryl group to form an aryl cation with or without participation of an external acceptor solvent; in homolytic dediazoniation it is electron transfer from an external donor.

We have chosen the term "nucleofugic homolytic leaving group" to describe a group possessing both nucleophilic character and the ability to release an electron[2]. In principle, it should be possible to quantitatively predict the reactivity of such particles towards diazonium ions with the aid of a dual-parameter equation. One parameter serves as a measure for the donor property of the particle, and the other one is the redox potential. The complex nature of the kinetics of homolytic dediazoniations will most likely be a great obstacle in the way of our obtaining comparable rate constants referring only to the radical generation step.

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therefore also be designated as an encounter complex, in spite of possible semantic confusion.
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Photochemical Rearrangements and Fragmentations of Alkenes and Polyenes

By Gerd Kaupp[*]

This article presents a systematic analysis of the numerous intramolecular reactions of electronically excited alkenes categorized according to substance class and reaction type. The rearrangements and fragmentations observed in simple alkenes are usually rediscovered in non-conjugated and conjugated dienes and polyenes, where they are accompanied by reaction types such as rearrangements involving several double bonds, cyclizations, and intramolecular cycloadditions. Geometrical factors largely determine which reaction of a series of energetically feasible competing processes actually takes place. The industrial syntheses of vitamin D utilize many of the reaction types to be discussed.

1. Introduction

Alkene photochemistry is an unusually complex and versatile field of study[1]. The reason lies in the generally high excess energies after absorption of light and the large number of basically possible deactivation processes still available even if attention is restricted to intramolecular photoreactions and the almost ubiquitous competing processes of luminescence, chemically non-productive deactivation, and *cis/trans* isomerization are disregarded. The wealth of existing material requires some kind of classification. There is still no theoretical concept available for reliable prediction of preferences between the numerous reaction types observed, although distinction between "allowed" and "forbidden" processes is now a closed chapter of chemistry[2]. Yet, arrangement of the material according to substance classes and reaction types permits a comprehensive treatment of preparative aspects in which common and distinguishing features of the individual types can be recognized. This could possibly further our understand-

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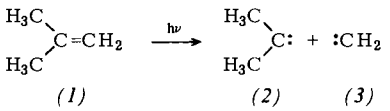
ing of processes occurring on transformation of electronic excitation energy into vibrational energy.

Photochemical syntheses are of particular value when it becomes possible in various cases to achieve a pronounced selectivity for one of the many possible reactions. The reaction conditions (cf. ref. [3]) and structural variation of the substrate can be used to modify or control the result of a reaction. Both approaches are used largely empirically and therefore require comparative experimentation. The present article is concerned mainly with reactions in liquid phase, which give good product yields or appear highly typical in some other way, and has a pronounced practical slant.

2. Monoenes

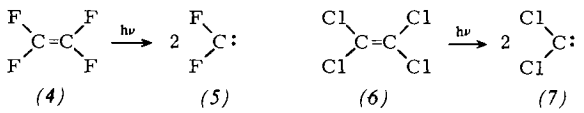
2.1. Cleavage of Double Bonds

Simple alkenes such as *(1)* (gas phase, $\lambda = 184.9$ nm) show only little tendency to undergo cleavage at the double bond to form two carbene fragments; most of the products are formed by dissociations of the C—H and C—C bonds[4].

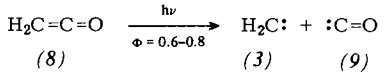


(1) *(2)* *(3)*

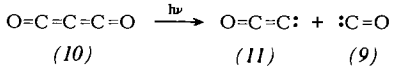
Double bond cleavage proceeds with better yields in polyhalogenated alkenes like *(4)*[5] and *(6)*[6] and in ketenes *(8)*[7] and carbon suboxide *(10)*[8].



(4) *(5)* *(6)* *(7)*

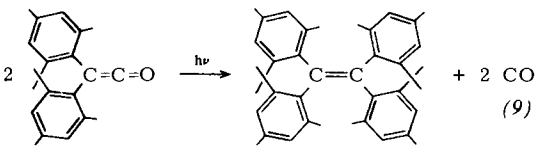


(8) *(3)* *(9)*



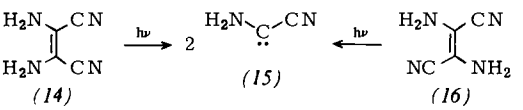
(10) *(11)* *(9)*

The resulting carbenes can be trapped as usual by added reactants, or they can dimerize. Thus, preparative interest attaches to the formation of *(13)* ($\lambda = 253.7$ nm)[9].



(12) *(13)* *(9)*

In the case of *(14)* and *(16)* double bond cleavage to give *(15)* could be accomplished at -196 °C[10]. However, this reaction type often appears to approach the limits of

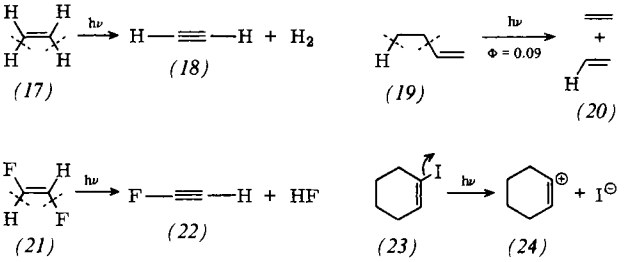


(14) *(15)* *(16)*

energetic feasibility in condensed phase. This is only rarely the case with the photocleavage of single bonds.

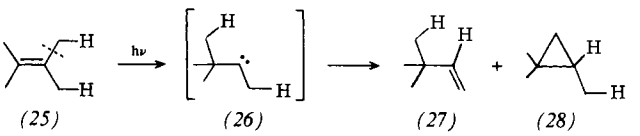
2.2. α-Cleavage

The photochemical cleavage of α bonds is widespread in the simplest alkenes. This is seen in the reactions of *(17)*[11], *(19)*[12], *(21)*[13], and *(23)*[14]. Formation of *(22)* was observed at as low a temperature as 10 K[13].

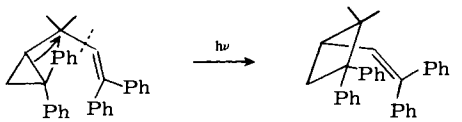


(17) *(18)* *(19)* *(20)* *(21)* *(22)* *(23)* *(24)*

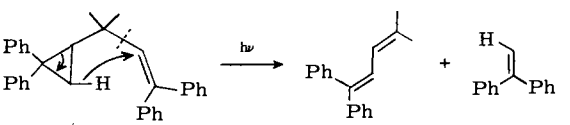
α-Bonds in more complicated molecules can also be cleaved by the action of light. Thus *(25)* gives *(27)* (17 %) and *(28)*



(25) *(26)* *(27)* *(28)*

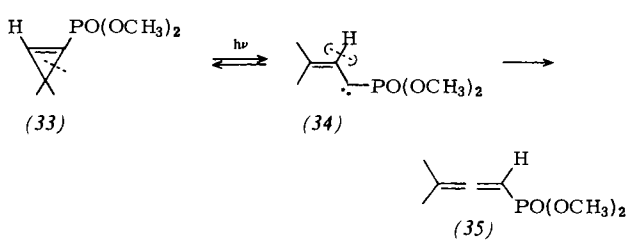


(29) *(30)*



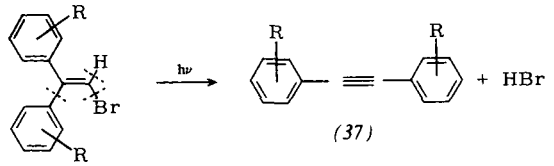
(29) *(31)* *(32)*

(24 %)[15], presumably *via* the carbene *(26)*; α-cleavages of *(29)* ($\lambda = 253.7$ nm) with rearrangement and fragmentation have been described as cyclopropyl-π-methane rearrangement[16]. α-Cleavage of *(33)*[17] gives the vinylcarbene *(34)*.



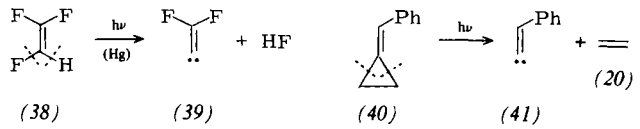
(33) *(34)* *(35)*

Formation of *(35)*[17] then also requires cleavage of an α-C—H bond. A total of three α bonds are cleaved on elimination of HBr from *(36)*. The yields of *(37)* vary between 50 and



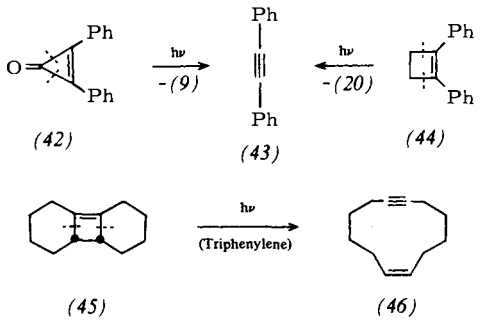
(36) R = o-, m-, p-OCH_3 (37)

86%[18]. The photoreaction of (36) could proceed *via* a vinylcarbene, like those from (38)[19] and (40)[20].



(38) (39) (40) (41) (20)

Other α-fragmentations can be achieved with cyclopropenones such as (42)[21] and cyclobutenes such as (44)[22] and (45)[2c,23]. It is especially remarkable that in dilute solution (44) is cleaved only to (43) and ethylene (20), and fails to form a (dihydro-)phenanthrene derivative or to undergo the ring opening to 2,3-diphenyl-1,3-butadiene which occurs



(42) (43) (44) (45) (46)

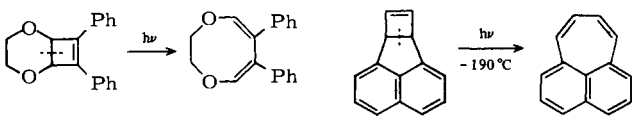
on heating to 100 °C. The α-cleavages described here are related to the long-known formation of alkyl and acyl radicals on photolysis of aldehydes and ketones[24].

2.3. β-Cleavage

After electronic excitation of alkenes, β bonds can be cleaved (again as in carbonyl compounds). This opens up a greater variety of reaction types than α-cleavage.

2.3.1. Ring Opening

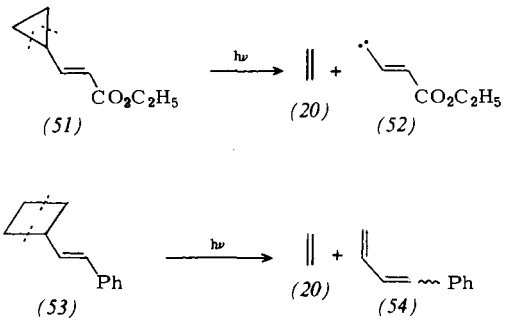
Photochemical ring opening of cyclobutenes to butadienes is comparatively rare. Synthesis of the dihydrodioxocin (48) (88%) is of preparative value[25]. Interestingly, (49) and related compounds in some cases react only from the second triplet level after absorption of two light quanta[26]. Furthermore, the slight tendency of cyclobutenes to undergo β-cleavage is significant if it is intended to perform [2+2] photocycloadditions with them[27].



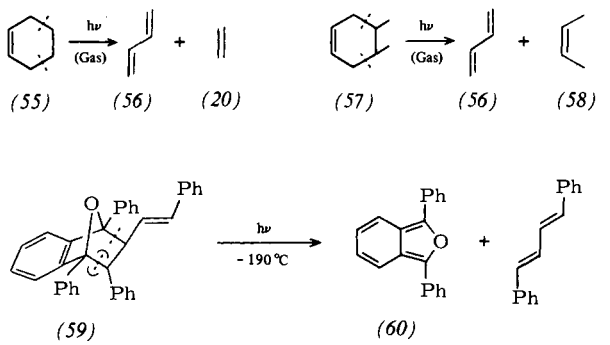
(47) (48), 88% (49) (50)

2.3.2. Fragmentations

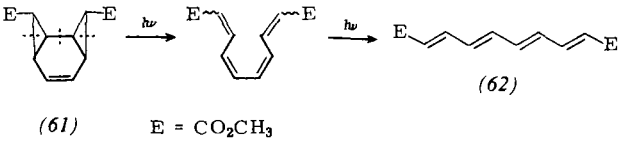
Photochemical cycloreversions of vinylcyclopropanes and vinylcyclobutanes lead to carbenes and alkenes, respectively. Compound (51) decomposes by cleavage of two β bonds. The carbene (52) then undergoes several secondary reactions (isomerization to the allene, to ethoxyfuran, and to ethyl cyclopropenecarboxylate)[28]. In the case of (53) a β and a γ bond are cleaved; this occurs even at −190 °C[29]. Further cycloreversions concern photochemical retro-Diels-Alder fragmentations of cyclohexenes. If such reactions are to be accomplished in solution [see, *e.g.* (55)[30] and (57)[31]] then quantum-consuming ring inversions must be suppressed by suitable substituents; (59) is an example[22,29]. The complicated cleavage of the eight-membered ring in the rigid, sterically hindered species (61) is to be classified as a [4+2+2] reaction[22].



(51) (20) (52) (53) (20) (54)



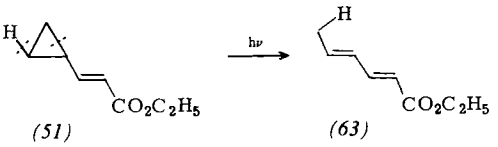
(55) (56) (20) (57) (56) (58) (59) (60)



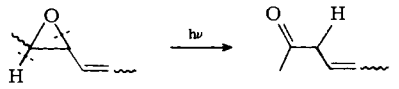
(61) E = CO_2CH_3 (62)

2.3.3. Opening of Three- and Five-Membered Rings with Substituent Migration

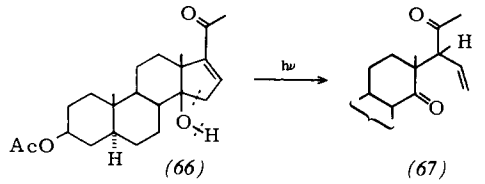
A reaction closely related to cycloreversion is the formation of open-chain isomers from odd-membered rings. Thus (51) reacts to give (63)[28]; of preparative significance are corresponding rearrangements of vinyloxiranes such as (64)[32]. In unsaturated five-membered rings, one or two β bonds can be photochemically cleaved, as shown by the reactions of (66)[33] and (68)[34].



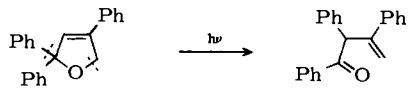
(51) (63)



(64) (65)



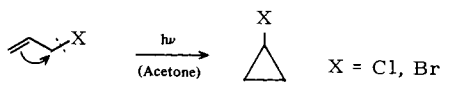
(66) (67)



(68) (69)

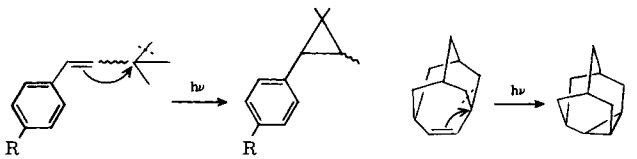
2.3.4. 1,2-Shifts

The β-cleavage of alkenes can be associated with a 1,2-shift of substituents; cyclopropane derivatives are obtained in this case. On irradiation in acetone, allyl chloride and allyl bromide give 17 and 10%, respectively, of cyclopropyl halides of type



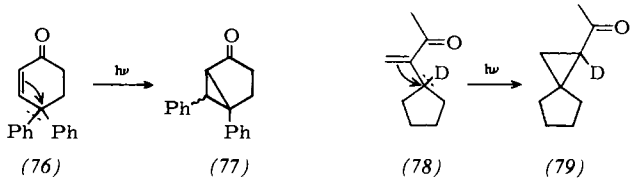
(70) (71) X = Cl, Br

(71)[35]. Like halogen atoms, the alkyl groups can migrate in *(72)*[36] and *(74)*[37], the phenyl groups in *(76)*[38], and the H (D) atoms in *(78)*[39].



(72) (73) (74) (75)

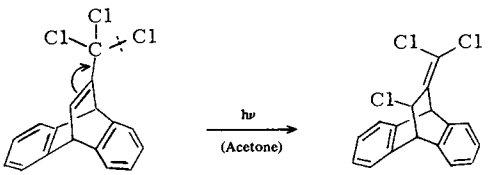
R = CN, H, OCH_3 *cis + trans*



(76) (77) (78) (79)

2.3.5. 1,3-Shifts

1,2-Shifts nearly always compete with allyl migrations (1,3-shifts), which also warrant synthetic interest. Thus double bonds can be pushed into exocyclic positions by migration

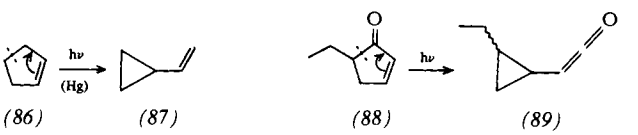


(80) (81), 95%



(82) (83) (84) (85)

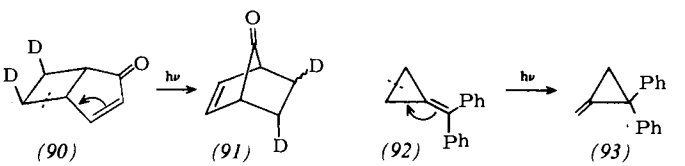
of halogen [cf. *(80)*][40] or H atoms [cf. *(82)* and *(84)*][41]; or ring contractions can take place to give energetic vinylcyclopropanes such as *(87)* and *(89)*, which release energy on reversion to cyclopentenes by valence-bond isomerization[42].



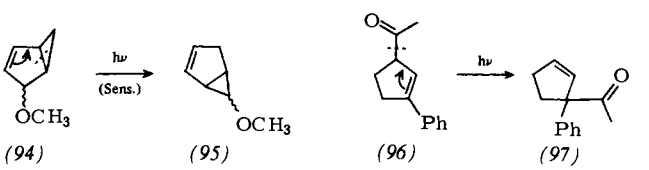
(86) (87) (88) (89)

cis + trans

Ring contraction of *(88)* is not stereospecific[43]. Also of interest are ring expansions as in *(90)*[44] and migrations of three-membered rings as in *(92)*[20] and *(94)*[45] by 1,3-shifts

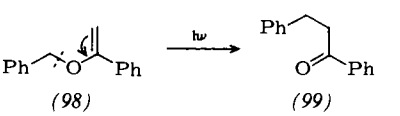


(90) (91) (92) (93)



(94) (95) (96) (97)

after direct or sensitized excitation. Some uncertainty surrounds the question whether 1,3-acyl shifts like that of *(96)*[46] follow excitation of the alkene or the carbonyl group. Moreover, 1,3-shifts are also of preparative significance in the



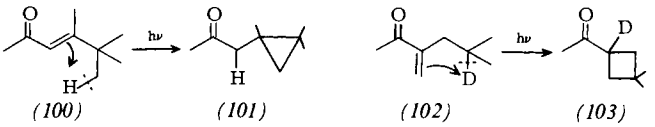
(98) (99)

transformation of enol ethers into ketones, as demonstrated by the reaction of *(98)*[47].

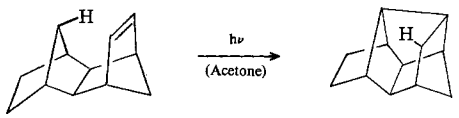
2.4. Intramolecular Hydrogen Transfer

If after electronic excitation β-, γ-, δ-, *etc.* hydrogen atoms are located in the proximity of a double bond, they can be transferred. Thus, the three-, four-, and five-membered rings in *(101)*[48], *(103)*[39,49], *(105)*[50], and *(107)*[51] are formed by intramolecular addition of C—H bonds. These

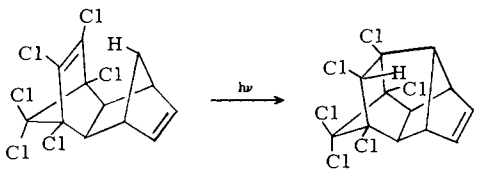
modes of reaction are favored by the geometry of the molecules in all known cases. The reactions probably proceed *via* diradicals after direct and sensitized excitation. A related reaction is observed in poly-1,2-butadiene (see Section 3.3).



(100) *(101)* *(102)* *(103)*

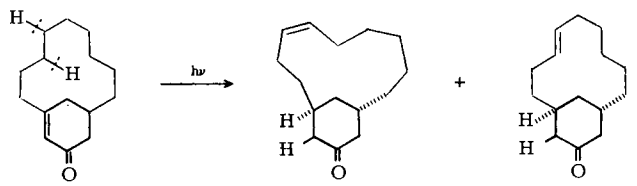


(104) *(105)*, 25%

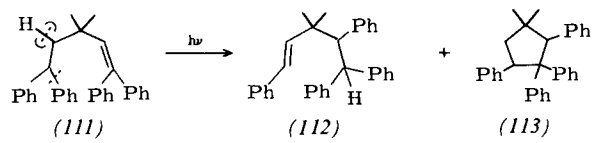


(106) *(107)*, 80%

Ring formation is not the only secondary reaction to ensue upon photochemical hydrogen transfer. Site exchange of a second hydrogen atom or of substituents can lead to formation of a new double bond while the original one is simultaneously saturated. Thus *(108)* gives *(109)* and *(110)* stereoselectively at the six-membered ring[52]. Compound *(111)* photolyzes to the isomer *(112)* in *tert*-butanol[53]; furthermore, addition of a C—phenyl bond to the double bond of *(111)* gives the cyclopentane derivative *(113)* (cf. Section 2.5)[54].

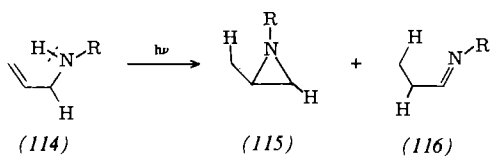


(108) *(109)* *(110)*

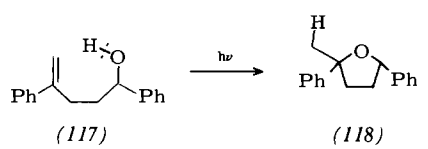


(111) *(112)* *(113)*

The concept of intramolecular hydrogen transfer is capable of extension. Thus both aziridine and imine formation occur in the case of the allylamine *(114)*[55]; addition of the O—H bond to the double bond of *(117)* leads to *(118)*[56].



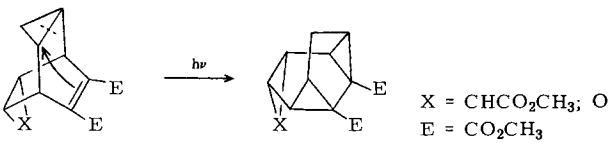
(114) *(115)* *(116)*



(117) *(118)*

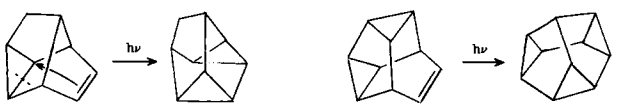
2.5. Intramolecular C—C Addition

As shown by the reaction of *(111)* to *(113)*, suitably oriented C—C bonds can undergo intramolecular photoaddition to double bonds. If the pertinent bond is part of a ring this type of reaction leads *via* ring opening to two new bonds. This is exploited for the synthesis of highly strained polycycles which are almost inaccessible by other methods. Thus in *(119)* the *exo*-oriented three-membered ring reacts to form the trishomobenzene derivative *(120)*[57]. Compound *(121)*



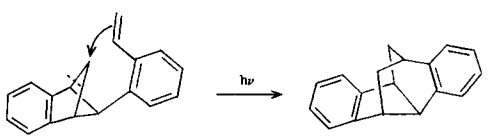
X = $CHCO_2CH_3$; O
E = CO_2CH_3

(119) *(120)*, quant.



(121) *(122)*, 30% *(123)* *(124)*, 5%

gives *(122)*[58], and *(123)* affords diademane *(124)*[59] possibly by this route. This reaction type is as expected not restricted to three-membered ring bonds. For example, *(125)* (accessible from *o,o'*-divinylstilbene) gives the polycyclic compound *(126)* by addition of a four-membered ring bond[60].



(125) *(126)*, 70%

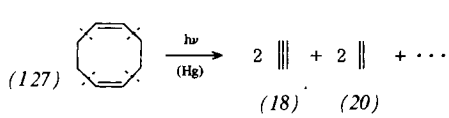
3. Non-conjugated Dienes

In principle, 1,4-, 1,5-, and 1,6-dienes should react just like simple alkenes after absorption of light. In addition, new pathways open up which involve both double bonds.

3.1. α-Cleavage

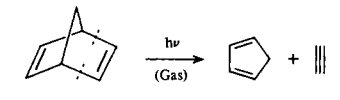
3.1.1. Fragmentations and Cycloreversions

On sensitized excitation (Hg^3P_1), 1,5-cyclooctadiene *(127)* decomposes to acetylene and ethylene, among other products. This fourfold α-fragmentation possibly proceeds in the gas phase *via* electronically excited 1,3-cyclohexadiene[61].

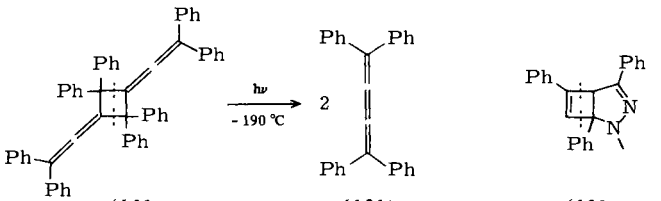


(127) *(18)* *(20)*

In 1,4-dienes, the action of light can rupture bonds which are situated α to one double bond and β to the other one. This can be utilized for retro-Diels-Alder reactions of norbornadiene *(128)*[62] and substituted norbornadienes (in competition with quadricyclane formation)[63]. Cleavage of *(130)*[64] to give *(131)* takes place even at −190 °C[29]. The



(128) (129) (18)

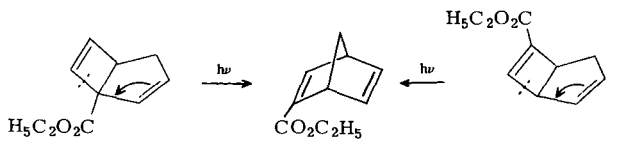


(130) (131) (132)

reaction of *(132)*[64a] can also be regarded as a [2+2] photocycloreversion.

3.1.2. 1,3-Shifts

1,3-Vinyl shifts can compete with fragmentation after α-cleavage of 1,4-dienes. The geometry of *(133)* and *(135)*[65] favors such a reaction course.

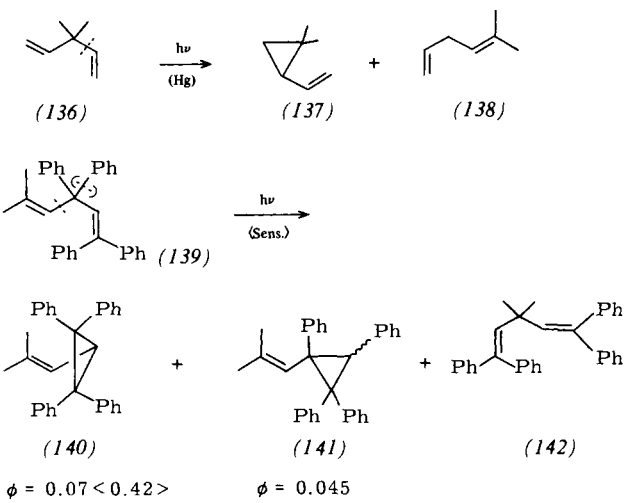


(133) (134) (135)

Further 1,3-vinyl shifts compete with di-π-methane rearrangement [cf. *(138)* and *(142)*].

3.1.3. Di-π-methane Rearrangement

α-Cleavage of 1,4-dienes can lead to 1,2-vinyl shifts in competition with fragmentation and 1,3-vinyl shifts. This reaction



(136) (137) (138)

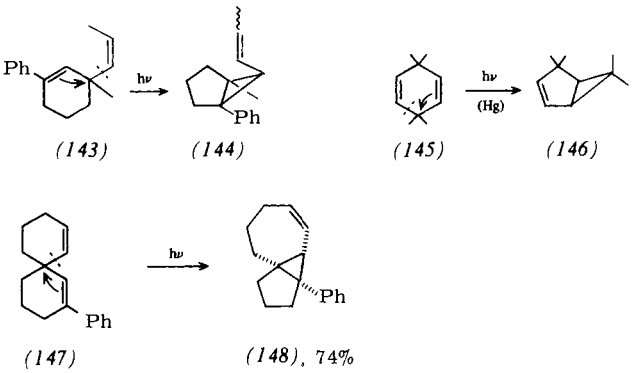
(139)

(140) (141) (142)

ϕ = 0.07 < 0.42 > ϕ = 0.045

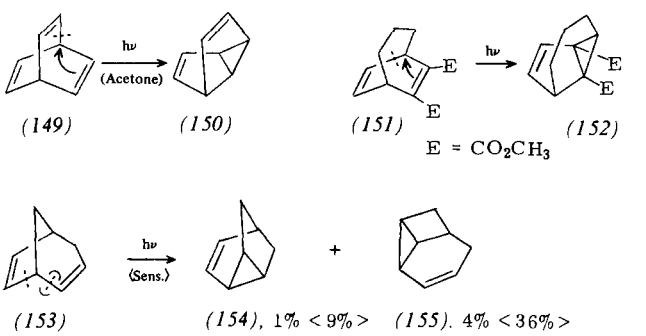
type is known as di-π-methane rearrangement (see ref. [1], pp. 413ff.) and, like β-cleavage with 1,2-migration (see Sections 2.3.4 and 3.2.1), leads to cyclopropane derivatives. Thus, the sensitized excitation of *(136)* leads *via* a 1,2-vinyl shift to *(137)* (35%) and *via* a 1,3-vinyl shift to *(138)* (30%)[42,66], and the direct or sensitized irradiation of *(139)* affords *(140)* (1,2-vinyl shift) and *(141)* (1,2-phenyl shift), together with *(142)* (1,3-vinyl shift)[67]. We cannot consider here the various mechanistic concepts that have been proposed to account for the course of singlet or triplet di-π-methane rearrangements[2b,2c,68,69]. It should be pointed out, however, that far-reaching changes in molecular geometry take place and the temporal sequence of α-cleavage and three-membered ring formation need not be the same for all starting compounds.

If the geometrical conditions do not favor intramolecular [2+2] cycloadditions (see Section 3.3), then interesting polycyclic compounds (always containing three-membered rings) can be synthesized from cyclic 1,4-dienes by 1,2-vinyl shifts. Thus direct excitation of *(143)* gives *(144)* non-stereospecifically[70], *(145)* is transformed into *(146)* on sensitized irradiation[71], and *(147)* gives *(148)*[72]. Compounds *(149)*[73] and *(151)*[74] permit important syntheses in polycyclic photochemistry. Direct or acetone-sensitized excitation of *(153)* gives the regioisomers *(154)* and *(155)*[75].



(143) (144) (145) (146)

(147) (148), 74%



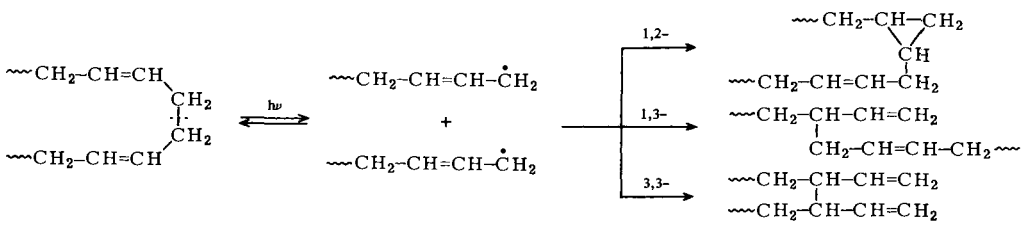
(149) (150) (151) (152)

E = CO_2CH_3

(153) (154), 1% < 9% > (155), 4% < 36% >

3.2. β-Cleavage

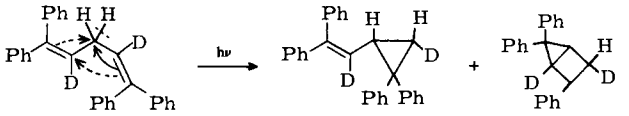
β-Cleavage of 1,5-dienes leads to two allyl radicals. This is shown by ESR studies on the photochemical degradation of poly-1,4-butadiene and poly-1,4-isoprene at −196°C[76].



The radicals are stabilized with considerable quantum yields by 1,2-shifts to form cyclopropane derivatives and recombination after the manner of 1,3- and 3,3-shifts according to the reaction scheme[77].

3.2.1. 1,2-Shift

Not only 1,5-dienes like poly-1,4-butadiene, but also 1,4-dienes, can react *via* 1,2-shifts (now no migration of the vinyl group as in the di-π-methane rearrangement; cf. Section 3.1.3). This was first demonstrated by the rearrangement of deuterium-labeled *(156)*. Formation of both *(157)* and *(158)*[78]

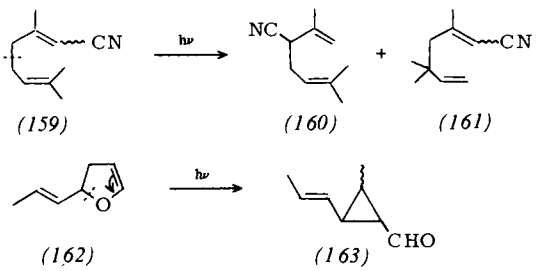


(156) *(157)* *(158)*

requires a 1,2-hydrogen shift. Accordingly, neither di-π-methane rearrangement nor intramolecular [2+2] cycloaddition take place.

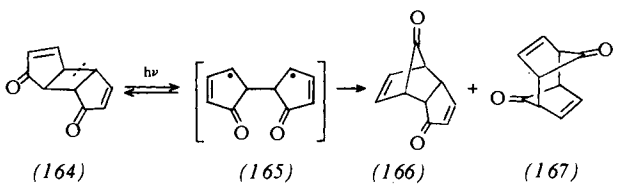
3.2.2. 1,3-Shift and 3,3-Shift

1,5-Dienes such as *(159)* which are essentially free from conformational restraints frequently undergo 1,3-shifts after electronic excitation[79]. Such behavior is observed with *(162)*[80] and in competition with *trans*-Cope rearrangement of *(164)*[81] [necessarily *via* the diradical *(165)*] to form *(166)* (1,3-shift) and *(167)* (3,3-shift). If photochemical 3,3-



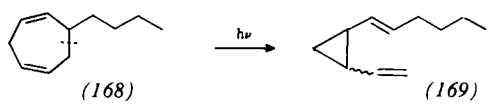
(159) *(160)* *(161)*

(162) *(163)*

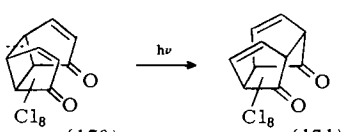


(164) *(165)* *(166)* *(167)*

shifts are to take place preferentially, then a favorable conformational situation must exist, as in *(168)*[82] and *(170)*[83]. The geometry of both compounds precludes intramolecular [2+2] cycloaddition[69].



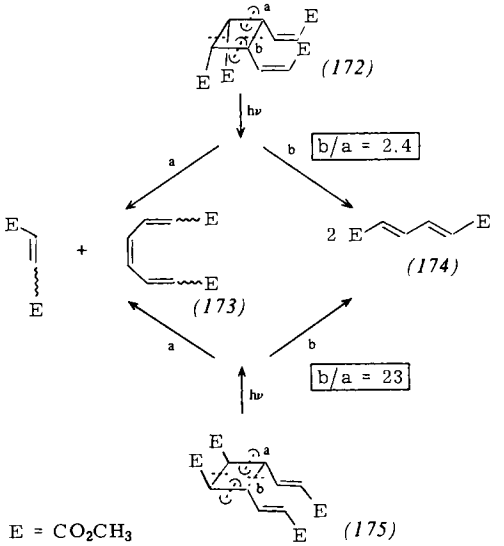
(168) *(169)*



(170) *(171)*

3.2.3. Cycloreversions

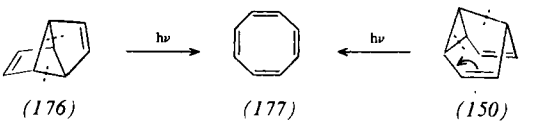
β-Cleavage of 1,5-dienes leads to [2+2] and [4+2] cycloreversions if the pertinent bond is part of a four- or six-membered ring. Thus 1,2-divinylcyclobutane derivatives like *(172)* and *(175)* fragment at −190°C. The orientation depends upon the degree of steric hindrance of the absorbing chromophore[22].



(172) *(173)* *(174)* *(175)*

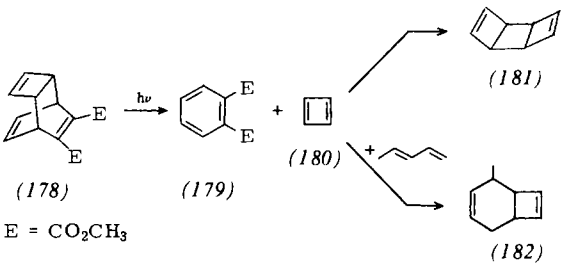
E = CO_2CH_3

Further β-cleavages leading to [2+2] and [4+2] cycloreversions are known to occur in the polycyclic compounds *(176)*[84] and *(150)*[85].



(176) *(177)* *(150)*

Particular mention should be made of the photo-retro-Diels-Alder reaction of *(178)*, which is shown by the dimerization and trapping products to involve formation of cyclobutadiene *(180)*[86]. (Low-temperature irradiation leads to intramolecular [2+2] cycloaddition[87]; cf. compound *(207)* having a similar skeleton in Section 3.3.)

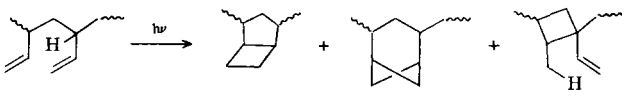


(178) *(179)* *(180)* *(181)* *(182)*

E = CO_2CH_3

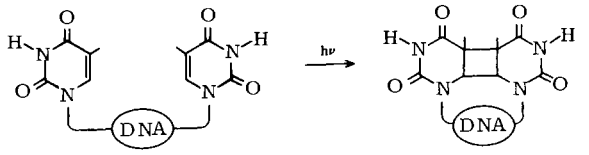
3.3. Intramolecular Cycloaddition

Intramolecular [2+2] cycloadditions of non-conjugated dienes are highly versatile and productive. They yield polycyclic compounds containing four-membered rings which are almost inaccessible by other pathways. Of comparable importance are aspects of polymer photochemistry and biophotochemistry. Thus on direct irradiation (253.7 nm) poly-1,2-butadiene loses its double bonds with a quantum yield of $\phi \approx 0.73$;

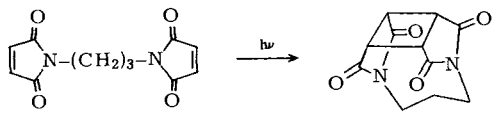


the 1,6-diene units form four-membered rings by parallel and crossed cycloaddition and γ-H transfer[77] (cf. Section 2.4). The same applies to poly-3,4-isoprene[77].

A photodynamic action is seen in the dimerization of pyrimidine bases, *e.g.* thymine, linked by strands of DNA, which also proceeds with sensitization. The resulting radiation

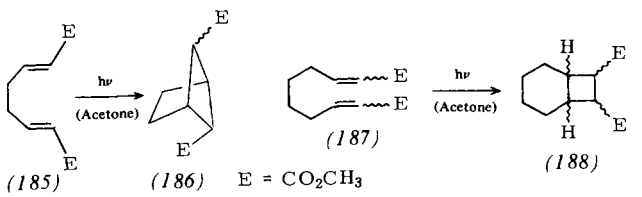


damage is only partly reversible. It can lead to mutations or to the death of the organism[88]. Numerous intramolecular models such as *(183)*[89] exist for these reactions; they show that the adoption of favorable conformations is indispensable.

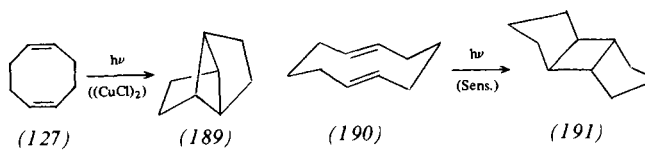


(183) *(184)*, quant.

Open-chain and monocyclic 1,5-dienes such as *(185)*[90] and *(127)*[91] prefer crossed cycloaddition, whereas 1,7- and 1,6-dienes such as *(187)*[92] and *(190)*[93], respectively, prefer

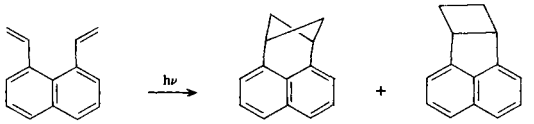


(185) *(186)* E = CO_2CH_3 *(187)* *(188)*



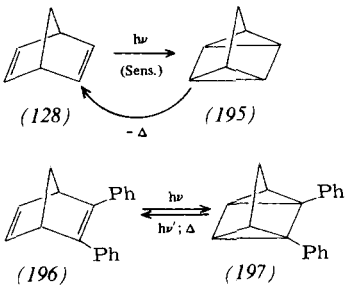
(127) *(189)* *(190)* *(191)*

parallel cycloaddition. This behavior most probably has mainly geometrical origins, and *(192)* accordingly undergoes both kinds of addition[94].



(192) *(193)* *(194)*

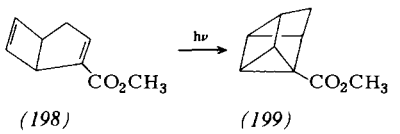
The geometrical requirements for cycloaddition by the kinetically elucidated intermediate mechanism[95] are well known in the case of polycyclic dienes[2c, 69]. Sensitized transformation of norbornadiene *(128)* into quadricyclane *(195)* has a quantum yield of 0.3—0.4 and can serve for storage of solar energy, since the chemically fixed energy (24 kcal/mol) can be liberated under the influence of heavy metal catalysts[96]. Numerous substituted norbornadienes such as *(196)* are photoreversibly converted into quadricyclanes on direct irradiation; this can usually be accomplished at −190 °C[69, 95].



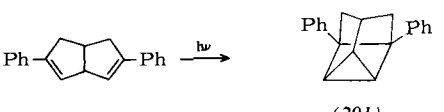
(128) *(195)*

(196) *(197)*

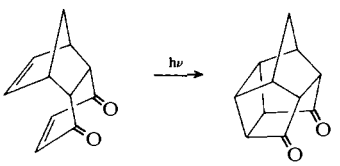
The range of structural variations of intramolecular [2+2] additions can only be hinted by a few examples [reactants *(198)*[97], *(200)*[98], *(202)*[99], *(204)*[100], *(207)*[101], *(210)*[102]]. (A recent survey is given in ref. [1], pp. 232ff.)



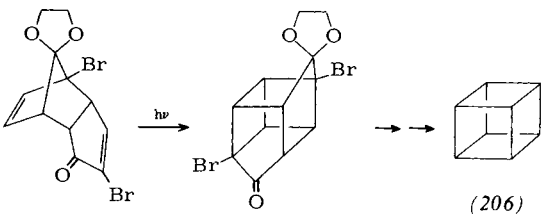
(198) *(199)*



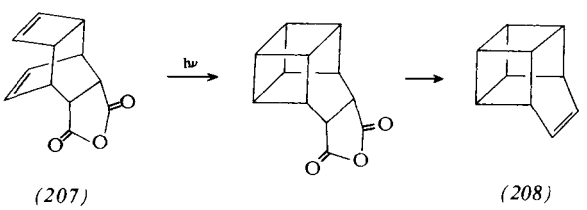
(200) *(201)*



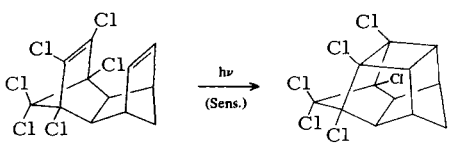
(202) *(203)*



(204) *(205)* *(206)*



(207) *(208)*

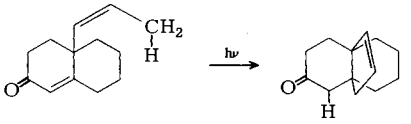


(209)

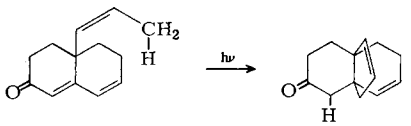
Particular mention should be made of the possibility of using 1,4-dienes with non-parallel double bonds, of the synthesis of cubane *(206)* and basketene *(208)*, and of the ecological aspects of the photoreaction of isodrin *(209)*[103].

3.4. Intramolecular C—H Addition

As in simple alkenes (see Section 2.4) non-conjugated dienes can engage in intramolecular addition of suitably oriented C—H bonds. This is used in photochemical syntheses of unsaturated [3.4.4]propellanes. Such reactions occur on short-wave irradiation ($\lambda = 253.7$ nm) of *(210)* and *(211)*[130a].



(210) 47%



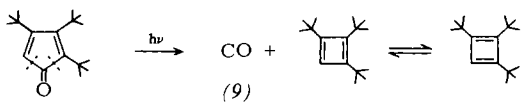
(211) 33%

4. Cross-conjugated Polyenes

Mainly historic reasons, but also their importance in the photochemistry of santonin[104], justify a separate account of cross-conjugated polyenes although the types of reactions involved do not differ fundamentally from those of monoenes or non-conjugated dienes. Only on progressing to non-alternant hydrocarbons do new reactions become evident, such as are found for conjugated polyenes.

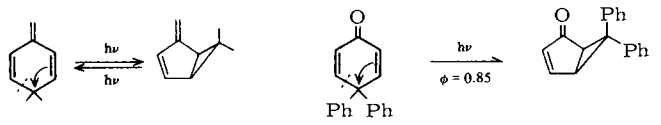
4.1. α-Cleavage

Photodecarbonylation of cyclopentadienones such as *(212)* [cf. the cyclopropenone *(42)*] at −196 °C leads *via* cleavage of two α bonds to cyclobutadiene derivatives[105]. Particular attention has been devoted to α-cleavages with 1,2-shift (cf.



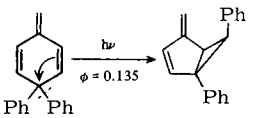
(212) CO + *(9)* *(213)*

Section 3.1.3) of cross-conjugated methylenecyclohexadienes such as *(214)* and cyclohexadienones such as *(216)*. They are transformed into homofulvenes[106] and homocyclopentadienones[107] on irradiation. The arrangement of substituents in *(215)* and *(217)* evidences migration of ring bonds. However, this is not always the case. Thus, irradiation of *(218)*

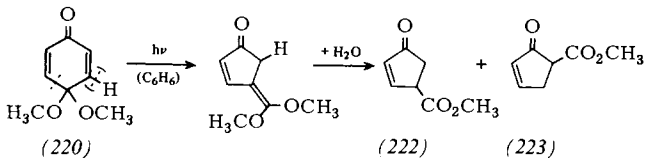


(214) *(215)* *(216)* *(217)*

proceeds with phenyl group migration to give *(219)*. The rearrangement of *(220)* is more complicated[108]: two α bonds migrate and the initial product *(221)* reacts with water to give *(222)* and *(223)* (15—20 %).

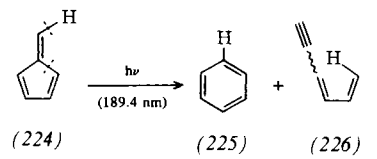


(218) *(219)*

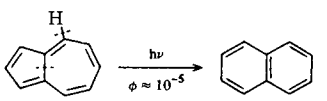


(220) *(221)* *(222)* *(223)*

Non-alternant hydrocarbons like fulvenes or azulenes also belong to the class of cross-conjugated polyenes. On photolysis of *(224)* in the gas phase[109] or of *(227)*[110], both α-C—H and α-C—C bonds are broken. The arenes *(225)* and *(228)* are formed by migration of the H atom along a double bond. Compound *(226)* probably arises by corresponding migration to the next-but-one C atom.



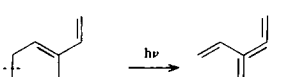
(224) *(225)* *(226)*



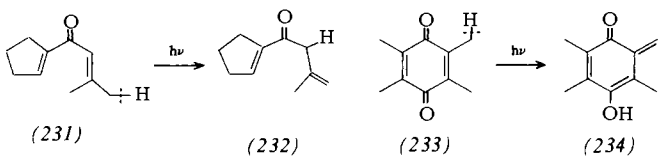
(227) *(228)*

4.2. β-Cleavage

The action of light on cross-conjugated polyenes can also lead to cleavage of β bonds provided that the structural conditions are satisfactory. This is demonstrated by the ring opening of *(229)*[111], the 1,3-H shift of *(231)*[112], and the 1,5-H shift of *(233)*[113]. The isomerization of *(235)*[114] can be

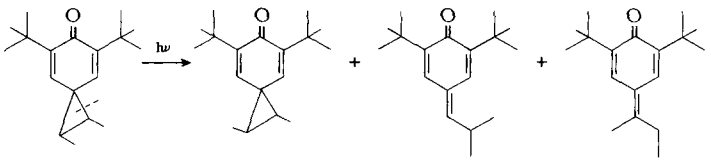


(229) *(230)*



(231) *(232)* *(233)* *(234)*

interpreted in a corresponding manner: compound *(237)* is formed by migration of a γ-methyl group, and *(238)* by migration of a γ-H atom.



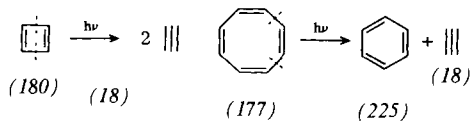
(235) (236) (237) (238)

5. Conjugated Dienes and Polyenes

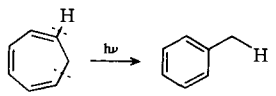
Numerous reactions of conjugated dienes and polyenes are vinylogous or cyclovinylogous to the processes already considered. In addition, structure-specific reactions become possible which involve two or more double bonds.

5.1. α-Cleavage

As in non-alternant hydrocarbons (see Section 4.1), internal and external α bonds of linearly conjugated polyenes can undergo cleavage following absorption of light. Two internal α bonds react in the case of cyclobutadiene *(180)* (at 8 K)[115] and cyclooctatetraene *(177)*[116], while two external α bonds (*i.e.* bonds lying outside the conjugated system) are affected in cycloheptatriene *(239)* (gas phase)[117].

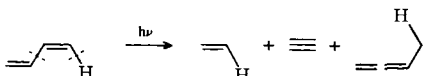


(180) (18) (177) (225) (18)

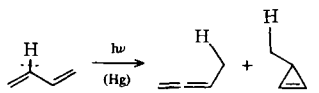


(239) (240), 98%

On gas-phase irradiation of *(56)* both fragmentation and α-H shift occur. The major products are *(18)*, *(20)*, and

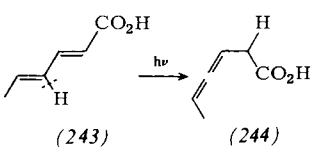


(56) (20) (18) (241)

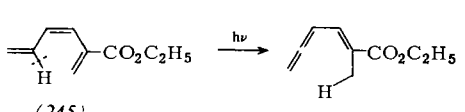


(56) (241) (242)

(241)[118], and on mercury-sensitized photolysis *(241)* and *(242)*[119]. In solution, the photolysis of sorbic acid *(243)*[120],

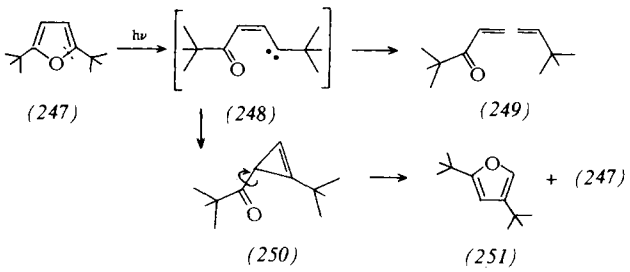


(243) (244)



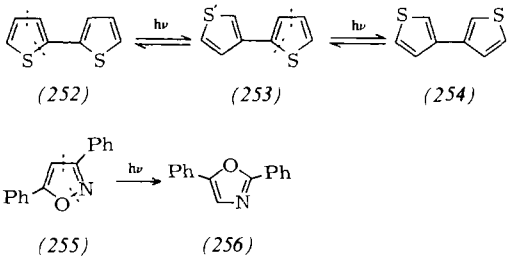
(245) (246), 70%

and that of 1,3,5-trienes such as *(245)*[121] or vitamin D_2 (see Section 5.9) affords allene derivatives. Allene derivatives can also arise on photolysis of furans such as *(247)*[112] if the carbene *(248)* presumably formed initially is stabilized by H migration. However, the reaction more often gives cyclopropene derivatives which can revert to furans. Thus *(247)*



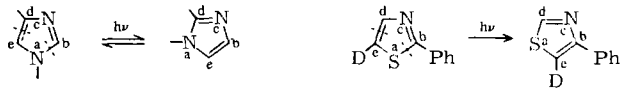
(247) (248) (249) (250) (251) + (247)

forms the isomer *(251)* [presumably *via (250)*][122]. Related reactions are seen in the photochemical rearrangements of pyrroles[123], thiophenes[123], and isoxazoles[124]. The reactions of *(252)* and *(255)* can be cited as examples. Imidazoles



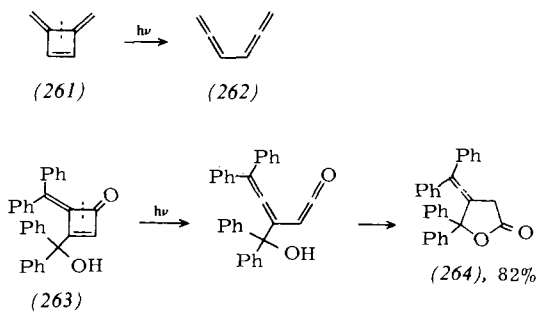
(252) (253) (254) (255) (256)

such as *(257)*[125] and thiazoles such as *(259)*[126] also undergo isomerizations involving α-cleavages after photoexcitation; however, no intermediates resembling *(248)* or *(250)* seem to be formed, but valence isomeric heterobicyclopentenes are postulated instead [compare the reaction of *(129)* in Section 5.5]. Overall, one single bond and one double bond are broken and formed afresh.



(257) (258) (259) (260)

The preparative versatility of α-cleavages is impressively demonstrated by the isomerization[29] of *(261)*[127] to bisallene *(262)*[128]. The methylenecyclobutenone *(263)* correspondingly reacts to give the keteneallene, which is transformed into the lactone *(264)* by intramolecular addition of the hydroxy group[129].



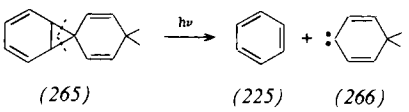
(261) (262) (263) (264), 82%

5.2. β-Cleavage

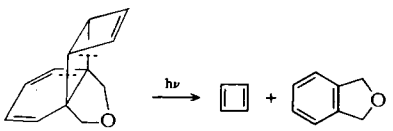
Photochemical cleavage of β bonds has been observed in many dienes and polyenes. This leads to fragmentations or isomerizations; interesting preparative applications exist for both reaction types.

5.2.1. β-Cleavage with Fragmentation

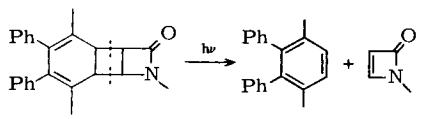
Cyclic dienes and trienes whose allylic C atoms also belong to another ring are suitable for the controlled production of reactive fragments which can be detected by spectroscopy. Characteristic reactions are those of *(265)*[130], *(267)*[131], *(269)*[132], *(272)*[133], *(274)*[134] and *(277)*[135]. After absorption of light, they proceed without further energetic activation and therefore take place at very low temperatures. The reaction course is unequivocally determined by geometrical factors[22]. The same applies to the synthesis of bullvalene *(280)*[136] and [16]annulene *(282)*[137]. In *(283)*, a compound having considerable conformational freedom, both fragmentation and valence isomerization are observed in the ratio a : b = 3 : 2[138]. For conformational reasons, *(285)* reacts by conrotatory opening of the bond common to both rings to give a diradical which reacts further to form not cyclodecatetraene but decapentaene *(286)* instead[139]. The success of [6+4] and [6+6] cleavages in *(274)* and *(277)* is related to the gain in steric freedom and the greatly limited conformational mobility in the reactant.



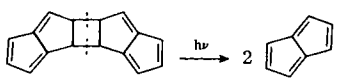
(265) *(225)* *(266)*



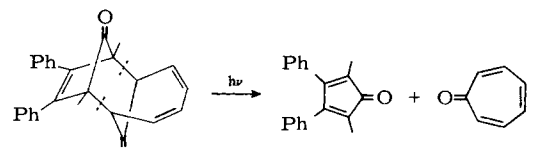
(267) *(180)* *(268)*



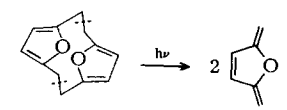
(269) *(270)* *(271)*



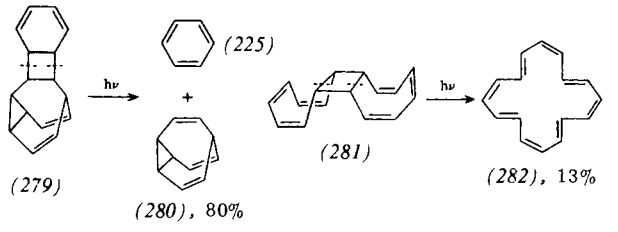
(272) *(273)*

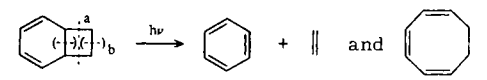


(274) *(275)* *(276)*

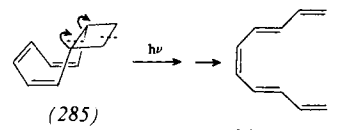


(277) *(278)*





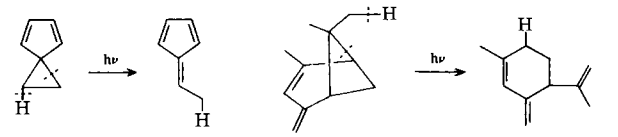
(283) *(225)* *(20)* *(284)*



(285) *(286)*, 50-80%

5.2.2. β-Cleavage with H Migration

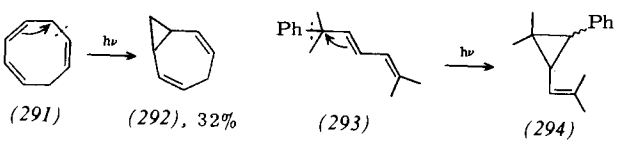
Comparatively complicated rearrangements take place if β- or γ-H atoms migrate after cleavage of a β bond. Such is the case with *(287)*[140] and *(289)*[141] which react *via* ring opening and formation of a further double bond. These reactions resemble those in Section 2.3.3.



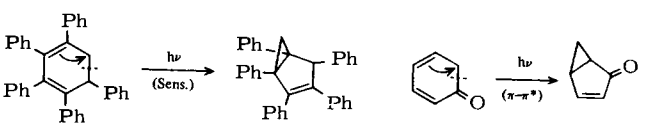
(287) *(288)*, 75% *(289)* *(290)*

5.2.3. β-Cleavage with 1,2-Shift

As with monoenes (Section 2.3.4) and 1,4-dienes (Section 3.2.1) three-membered ring syntheses are also feasible with open-chain and cyclic 1,3-dienes. Vinyl[142], phenyl[143], alkyl[144], and acyl groups[145] can migrate, as shown by the examples *(291)*, *(293)*, *(295)*, and *(297)*, respectively. These reactions compete with 1,3-shifts among other processes.



(291) *(292)*, 32% *(293)* *(294)*

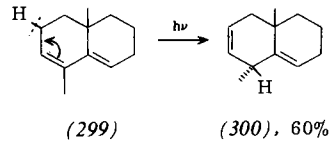


(295) *(296)* *(297)* *(298)*

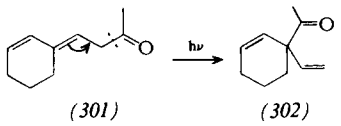
5.2.4. 1,3-Shift

Allyl migrations shorten the conjugated chain in polyenes. Apart from the migration of H atoms as in *(299)*[146] and acyl groups as in *(301)*[147], interest attaches to the far-reaching structural changes attending shifts of ring bonds in polycyclic compounds. Representative reactions are the rearrange-

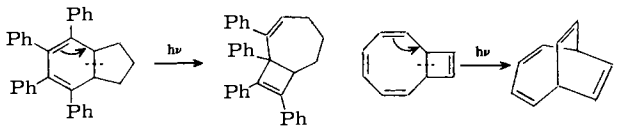
ments of *(303)*[148], *(305)*[149], *(307)*[150], and *(309)*[151]. It has not yet been established whether all these reactions proceed as one-quantum processes; however, the formulation chosen is especially clear.



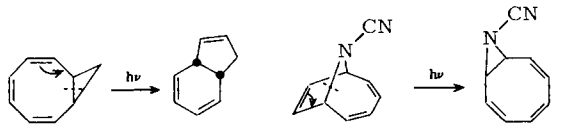
(299) *(300)*, 60%



(301) *(302)*



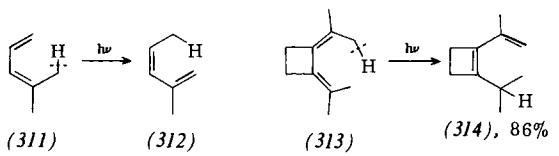
(303) *(304)*, 95% *(305)* *(306)*



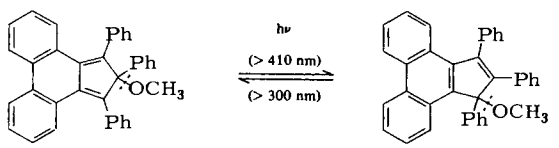
(307) *(308)*, 12% *(309)* *(310)*

5.2.5. 1,5-Shift

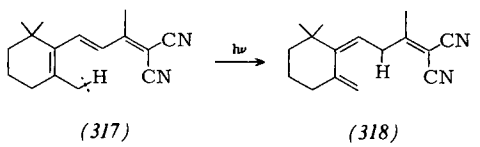
If 1,5-shifts are to effectively compete with allyl migrations then those conformers must be favored in which the reaction centers are spatially proximate. Thus the H atoms of *(311)*[152] and of *(313)*[153] and the methoxy group of the photochromic



(311) *(312)* *(313)* *(314)*, 86%



(315) *(316)*

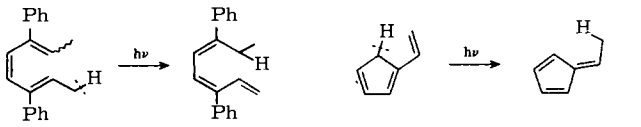


(317) *(318)*

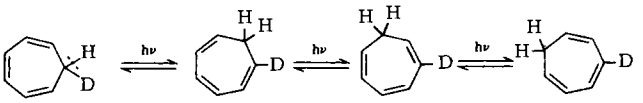
system *(315)*⇌*(316)*[154] migrate to the end of the conjugated system. The 1,5-shift is also favored in the triene *(317)*[155]. Once again, geometric factors play a decisive role[2c].

5.2.6. 1,7-Shift

Conformational conditions are even more important for 1,7-shifts. This mode of reaction can be promoted by bulky



(319) *(320)* *(321)* *(322)*, quant.

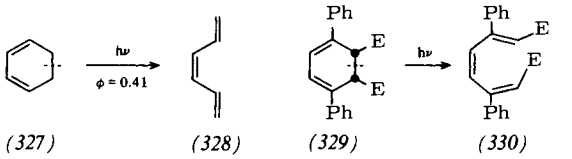


(323) *(324)* *(325)* *(326)*

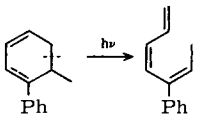
substituents, as in *(319)*[156], and by incorporation of double bonds in rings. Thus *(321)* reacts to give the fulvene *(322)*, and irradiation of *(323)* initially yields *(324)*. The latter product then forms *(325)* and ultimately *(326)*[157,158].

5.2.7. Ring Openings

1,3-Cyclohexadienes and higher dihydroannulenes can be transformed into extended polyenes by cleavage of the β-C—C bond. These reactions are cyclovinylogous to cyclobutene ring opening and open up manifold preparative possibilities. Formation of 1,3,5-hexatriene is favored above all when the substrate preferentially adopts the half-chair conformation rather than the half-boat conformation (see the reactions of lumisterol and ergosterol as against those of pyrocalciferol and isopyrocalciferol in Section 5.9). The reactions of *(327)*[159], *(329)*[156], and *(331)*[160] are typical for this kind of ring opening. Although preparative application generally affords



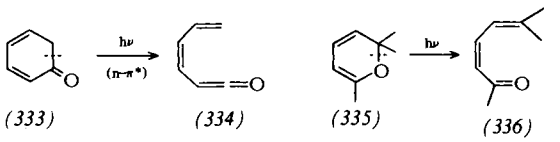
(327) *(328)* *(329)* *(330)*



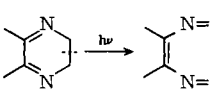
(331) *(332)*

E = CO_2CH_3

a mixture of stereoisomers, and the hexatrienes immediately undergo further photolyses (*e.g.* Section 5.7), it can nevertheless be demonstrated that ring opening is geometrically favorable and initially leads to *(328)*, *(330)*, and *(332)*, respectively. Incorporation of heteroatoms extends the scope of the reaction, as shown by the examples *(333)*[145], *(335)*[161], and *(337)*[161,162]. Moreover, the following selection of reactions

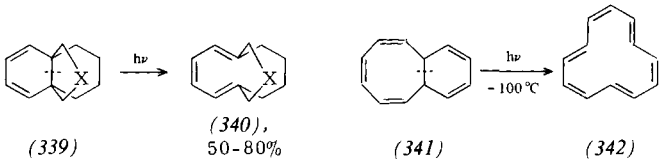


(333) *(334)* *(335)* *(336)*

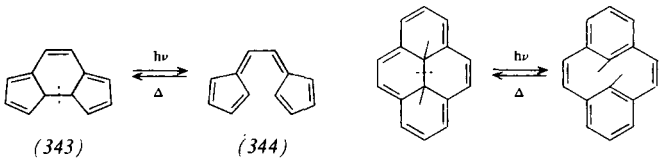


(337) *(338)*

demonstrates that ring opening by cleavage of β-C—C bonds is a suitable method for the synthesis of cyclic polyenes and of annulenes. Compound *(340)*[163] possesses two bridgehead double bonds. [12]Annulene *(342)*[164] must be prepared at low temperatures. Compound *(343)*[165] shows photochromic behavior, and the 16π-electron system *(345)*⇌*(346)*[166] represents an example of negative or inverse photochromism.



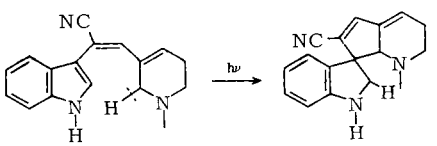
(339) *(340)*, 50-80% *(341)* *(342)*



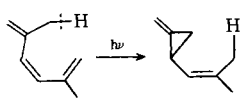
(343) *(344)* *(345)* *(346)*

5.3. Intramolecular C—H Addition

Like simple alkenes (Sections 2.4 and 3.4), conjugated polyenes can also undergo intramolecular addition of suitably oriented C—H bonds. This is known to occur in 1,3,5-trienes with an alkyl group attached to C-2. The indole double bond of *(347)* reacts in this way to give the spiro-compound *(348)*[167]. In contrast, the reaction of *(349)* to form *(350)*[168]



(347) *(348)*

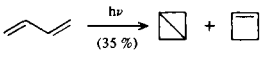


(349) *(350)*

comprises a 1,4-addition of the C—H bond to the 1,3-diene component of the polyene system. The synthetic potential of these reaction types does not appear to be exhausted. Formation of toxisterols *(420)*, most likely by photolysis of precalciferol *(410)* (see Section 5.9, and ref.[168c]), corresponds to the 1,2-addition reaction of *(347)*.

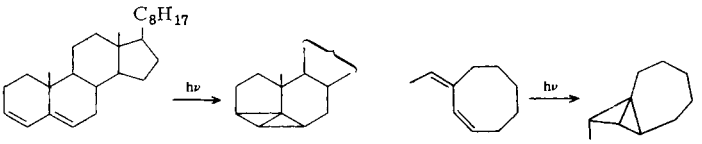
5.4. Bicyclobutane Formation

Irradiation of *(56)* leads to α-cleavage (see Section 5.1) and also to valence isomerization; the products are bicyclobutane *(351)* and cyclobutene *(352)*. Bicyclobutane formation is clearly disfavored although the compound can arise from the predominant *s-trans* conformation of *(56)* and does not require the higher-energy *s-cis*-conformer. The ratio of the yields of *(351)*/*(352)* is 1:16 in isooctane, 1:7 in ether, and 1:6 in ether in the presence of $(CuCl)_2$[169]. Cyclobutene ring closure is impossible in 3,5-cholestadiene *(353)*, which has fixed



(56) *(351)* *(352)*

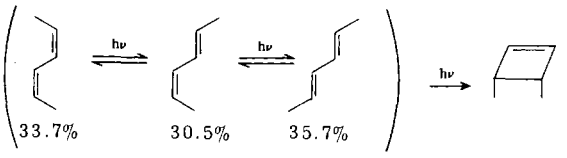
s-trans conformation, and the bicyclobutane *(354)* is formed in high yield[170]. The combination of exo- and endocyclic double bonds in *(355)* likewise facilitates the synthesis of *(356)*[171].



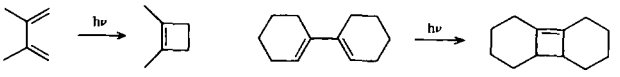
(353) *(354)*, 98% *(355)* *(356)*

5.5. Cyclobutene Ring Closure

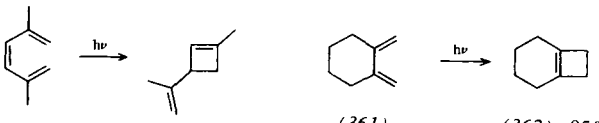
In open-chain 1,3-dienes, cyclobutene ring closure should be conrotatory for geometrical reasons, but disrotatory in cyclic 1,3-dienes (at least up to the seven-membered ring)[2c]. As a reaction compelled to proceed in one step, this cyclization has been the subject of detailed quantum mechanical calculations[2a,172]. In practice, however, the stereochemical result is influenced by generally fast *E*/*Z* isomerizations of the starting dienes. 2,4-Hexadiene (mixture of isomers) reacts to give *cis*-dimethylcyclobutene[173]; the synthesis of the parent compound *(352)* has already been mentioned in the preceding



Section. The yields of cyclobutenes are higher when the presence of substituents or rings favors the *s-cis* conformations of the dienes [*(357)*[174], *(359)*[174], *(349)*[168a,b]] or forces such conformations [*(361)*[175]] (examples from vitamin D photochemistry are given in Section 5.9).

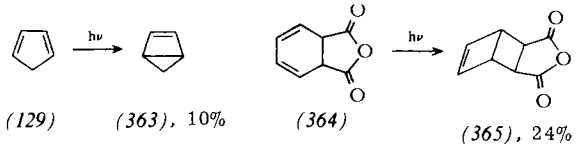


(357) *(358)*, 71% *(359)* *(45)*, 43%

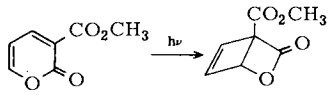


(349) *(360)* *(361)* *(362)*, 95%

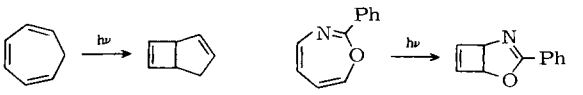
Cyclobutene ring closures are numerous in cyclic 1,3-dienes[176]. The syntheses of *(363)*[177], *(365)*[178] (the starting material for Dewar benzene), and *(367)*[179] (that for methyl cyclobutadienecarboxylate), and ring contractions in cycloheptatrienes such as *(239)*[176] and corresponding heterocycles, *e.g.* *(369)*[180], warrant particular interest. The tendency to form cyclobutenes seems most pronounced in seven-membered



(129) (363), 10% (364) (365), 24%



(366) (367)

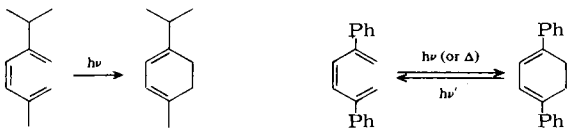


(239) (368), 50% (369) (370)

ring systems[181]. 1,3-Cyclohexadiene derivatives in the half-boat conformation (see Sections 5.2.6 and 5.9) also seem well suited for this reaction type. At moderately high temperatures almost all cyclobutenes regenerate the starting dienes with liberation of energy.

5.6. 1,3-Cyclohexadiene Ring Closure

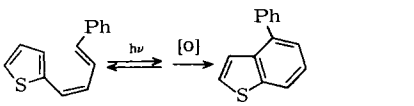
On photoexcitation, suitable 1,3,5-hexatrienes having a central *cis*-double bond cyclize not only to vinylcyclobutenes (cf. Section 5.5) but also to 1,3-cyclohexadienes. Substituents in position 2, as in *(371)*[168a,b] and *(373)*[182] are essential for good yields in the case of acyclic compounds. The necessary *s-cis,s-cis* conformers are also favored by introduction of one



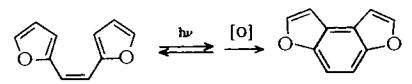
(371) (372) (373) (374)

or more double bonds into rings. This is utilized in the photolysis of precalciferol (see Section 5.9) and the syntheses of *(376)*[183] and *(378)*[184]. In the two last-mentioned cases, the reversible cyclization is followed by an oxidation step (with O_2, I_2, *etc.*). The principal application of this reaction lies in the synthesis of (dihydro-)phenanthrenes from *cis*-stilbenes with participation of benzene rings[185].

The ring contraction of annulenes and similar compounds is also of interest in connection with photolysis of alkenes.

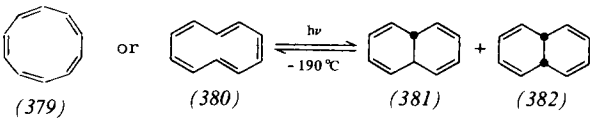


(375) (376)

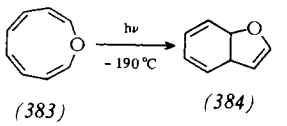


(377) (378)

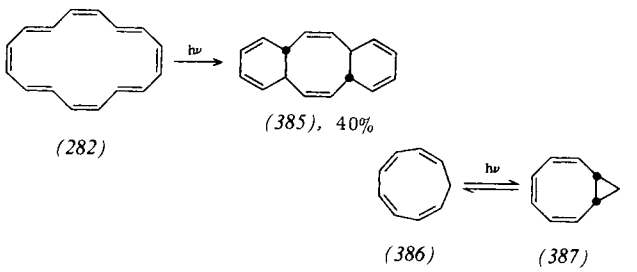
Compounds *(379)* or *(380)*[186] and *(383)*[187] form bicyclic products, whereas [16]annulene *(282)* undergoes double ring closure to give the tricyclic compound *(385)*[188]. Finally, unlike *(383)*, cyclononatetraene *(386)* is transformed into the cyclooctatriene derivative *(387)*[189] by cyclovinylogous ring closure.



(379) (380) (381) (382)



(383) (384)

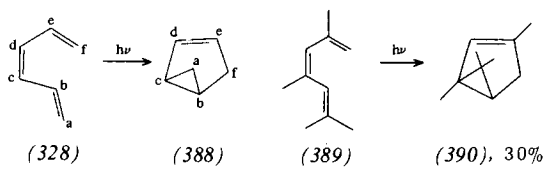


(282) (385), 40% (386) (387)

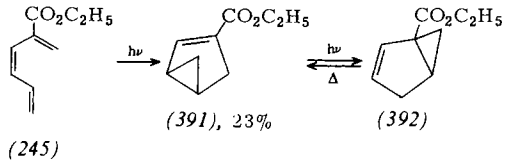
In view of the excess energy present after absorption of light, the observed selectivities are most probably once again conformational in origin.

5.7. Bicyclo[3.1.0]hexene Formation

1,3,5-Hexatrienes with a central *cis* double bond can generally undergo valence isomerization to bicyclo[3.1.0]hexenes, as is known to occur on formation of suprasterol from vitamin D_2 (see Section 5.9). This type of reaction is vinylogous to the formation of bicyclobutane from 1,3-dienes (Section 5.4)[190] and can be accomplished with *(328)*[191], although the yields are better with *(389)*[192] or *(245)*[121,193] since the conformers required for reaction are present in higher

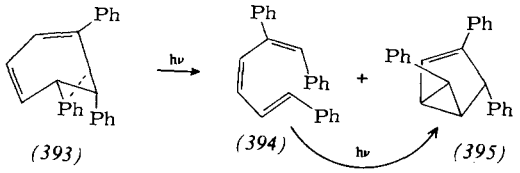


(328) (388) (389) (390), 30%



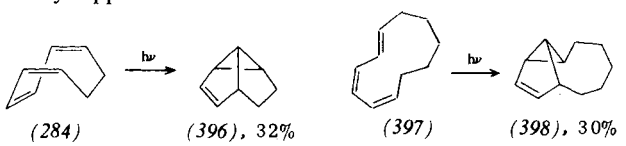
(245) (391), 23% (392)

equilibrium concentrations[2c,168a,b]. There is often no need to isolate the hexatrienes during preparation of the bicyclohexenes; instead, 1,3-cyclohexadienes such as *(393)* can be used as starting materials[194]. Compound *(395)* is also formed by photolysis of isolated *(394)*[194]. It remains to be established whether the β-cleavage of *(393)* with 1,2-shift contributes to the formation of *(395)* (cf. Section 5.2.3).

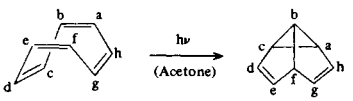


(393) (394) (395)

Cyclic polyenes such as *(284)*[195], *(177)*[196], and *(397)*[197] are also able to form bicyclo[3.1.0]hexenes. It appears to have been proved that the three-membered ring is formed before the five-membered ring in the synthesis of *(398)*[197]. However, it is uncertain whether this sequence always applies.



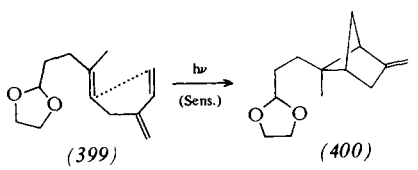
(284) *(396)*, 32% *(397)* *(398)*, 30%



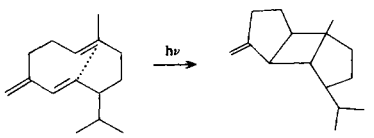
(177) *(150)*, 12%

5.8. Intramolecular Cycloadditions

Intramolecular [2+2] cycloadditions of polyenes are utilized in the synthesis and transformations of sesquiterpenes of importance as fragrances and flavors. Thus the cross-photocycloaddition of *(399)* to give *(400)* is the starting point of a synthesis of α- and β-*trans*-bergamotene[198]; germacrene-D *(401)* is converted by parallel addition into β-bourbonene *(402)* on direct irradiation[199].

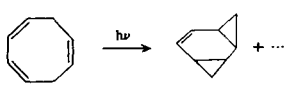


(399) *(400)*



(401) *(402)*

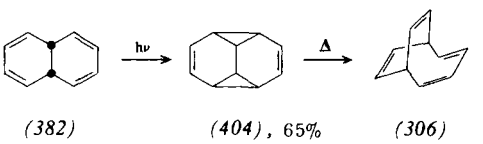
Intramolecular [4+2] cycloaddition of *(291)* is accompanied by various side reactions [*e.g.* giving *(292)*[138,200]].



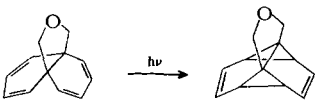
(291) *(403)*, 10%

Good yields are obtained from the [4+4] cycloaddition of *(382)* at −100°C to give *(404)*, which is transformed thermally into *(306)*[201]. Even more productive is the photoreaction of the propellane *(405)* at −78°C[202]. Above all, the last-named photocycloadditions appear to profit from an especially favorable geometrical situation.

Bispyrones[203] and 1,2,4-triazolo[4,3-*a*]pyridines[204] linked together by alkyl chains of various lengths contain



(382) *(404)*, 65% *(306)*



(405) *(406)*, 95%

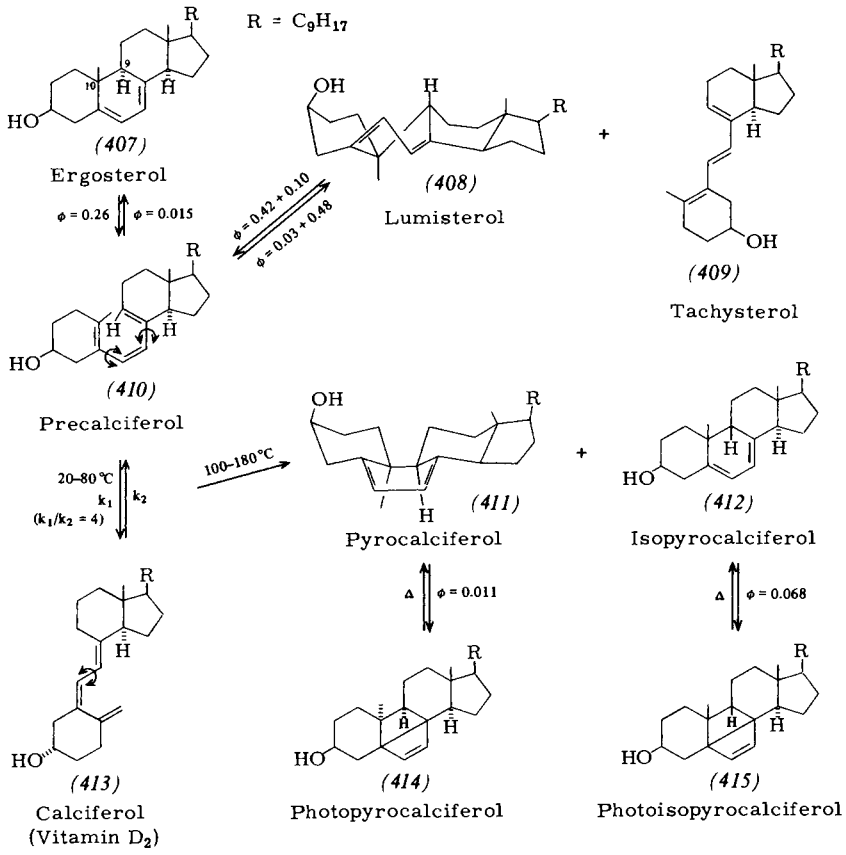
two separate polyene systems which react intramolecularly with each other by [2+2], [2+4], and [4+4] addition after absorption of light. These are borderline cases between intra- and intermolecular reactions.

The intramolecular [2+2] photocycloadditions of double bonds conjugated *via* two arene rings in *o,o'*-bis(2-arylvinyl)biphenyls, which lead to *trans,trans,trans*-1,2-diaryl-1,2,2a,10b-tetrahydrocyclobuta[*l*]phenanthrenes[205], are special cases.

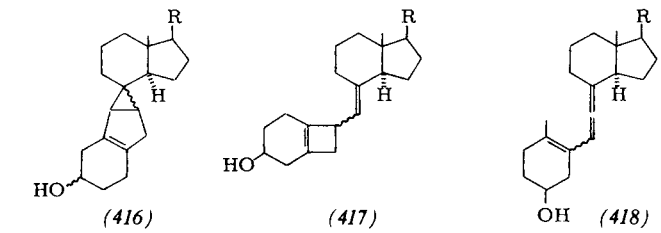
5.9. Photochemistry of Vitamin D

Conformational analysis acquired great importance in the complicated transformations occurring in the vitamin D series[206]. The industrial production of *(413)* (calciferol, vitamin D_2) involves irradiation of ergosterol *(407)* [preferred half-chair conformation as in *(408)*] generally in cooled ether solution. Opening of the cyclohexadiene ring results in conrotatory[2b] formation of precalciferol *(410)* which rearranges by a 1,7-H shift to calciferol *(413)* above 20°C. This product crystallizes and is separated off. The mother liquors contain *(407)*, *(408)*, and *(409)*. These compounds equilibrate with *(410)* on photolysis and can therefore be recycled to the process. In the photochemical cyclizations of precalciferol *(410)* the preferred lowest-energy *cZc*-helical conformation is responsible for the *trans* relationship of the substituents in positions 9 and 10 of *(407)* and *(408)* (conrotation). In contrast, *(411)* and *(412)* (formally disrotatory from precalciferol onwards) are obtained on heating of the 4:1 equilibrium mixture of *(413)* and *(410)*. Under these circumstances it appears that energetic conformers present in low concentrations play an active role and cyclize with a lower activation energy; similar behavior has been deduced from analysis of orbital symmetry for ring closures of hexatrienes[2b]. Unlike ergosterol *(407)* and lumisterol *(408)*, pyrocalciferol *(411)* and isopyrocalciferol *(412)* (with a half-boat conformation) undergo geometrically favorable cyclobutene ring closure to give the products *(414)* and *(415)* on irradiation, which revert to *(411)* and *(412)* on heating.

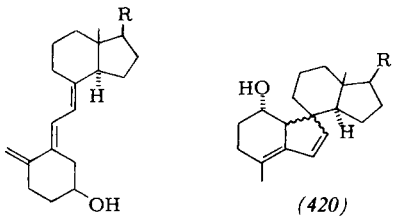
The need for cooling during photolysis of *(407)* and subsequent warming in order to form *(413)* is explained by the light sensitivity of *(413)*. As expected for *cZt* conformers, irradiation of *(413)* gives *(416)* (bicyclohexene formation), *(417)* (cyclobutene ring closure, two stereoisomers), *(418)* (α-H shift, two stereoisomers), and *(419)* (geometrical isomerization); some of these compounds are toxic. Furthermore, irradiation of *(407)*/*(410)* affords the toxisterols *(420)* [intramolecular C—H addition of *(410)*, three stereoisomers] as well as the fragmentation products *(421)*, *(422)* [α-cleavage of *(413)*], and *(423)*, *(424)*[207] [α-cleavage of *(410)*].



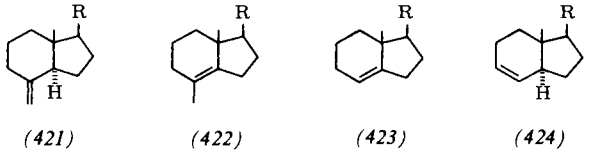
The transformation of *(407) via (410)* into vitamin D_2 *(413)* corresponds to the analogous photoreaction of 7-dehydrocholesterol *via* previtamin D_3 to form vitamin D_3. The latter is produced on a large scale as a food additive[208].



Suprasterol I and II



5,6-*trans*-Calciferol — Toxisterol



6. Outlook

The lively development of alkene photochemistry[209] which gathered considerable momentum in recent years has led to a large variety of reaction types. Many of them can be exploited in preparative work and on an industrial scale, or possess biological or ecological importance. No doubt other valuable types of reactions will be discovered which compete with those described in the present report. Classification of the available material according to compound classes and chemical results is no substitute for continued mechanistic and theoretical effort. However, such a classification provides a very convenient basis for a balanced treatment of the diverse and complex modes of reaction, without being overly influenced by the mere number of presently known examples. In this way valuable evidence is obtained concerning product-determining effects in photochemical deactivations, and questions of stereoselectivity as well as those of orientation- and regioselectivity can be approached empirically without requiring absolute calculations on the basis of quantum mechanical models.

Comparisons between characteristic examples of all known reaction types underline the unique features of special cases. Far from being a disadvantage, this procedure is a prerequisite for success in searching for new reaction types and in enhancing product yields by chemical modification or variation of reaction conditions. Conversely the approach adopted reveals which cases will give poor yields at best, owing to the excessive number of equally probable deactivation processes. A look at the possible modes of reaction can be just as important for settling unsolved problems as experimentally based mechanistic knowledge. Further practical applications and

a deeper understanding of alkene photolysis will doubtless require more detailed consideration of conformational effects.

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Selective Reactions with Organoaluminum Compounds

By Hisashi Yamamoto and Hitosi Nozaki[*]

With the aid of selected examples an overview is given of the development trends in highly discriminative reactions using organoaluminum compounds. 1) Isomerization of substituted oxiranes into allyl alcohols has been effected both stereo- and regioselectively by means of a new organoaluminum reagent, diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP); this reaction which provides a new route for the regiospecific transformation of allyl alcohols into 1,3-dienes. 2) A novel nonenzymic heterolysis of allylic phosphates of terpenoids has been effected by organoaluminum compounds and has enabled development of a new method for the selective synthesis of cyclic terpenes. 3) The reductive condensation of α-haloketones with carbonyl compounds in the presence of diethylaluminum chloride and zinc affords β-hydroxycarbonyl derivatives in good yields with exclusion of undesired self-condensations products.

1. Introduction

The problem of devising general synthetic methods for the selective or specific transformation of functional groups remains a major challenge despite extensive studies in this area for many years. During the past few decades the role of organometallic compounds in synthetic chemistry has become increasingly apparent. Particularly noteworthy has been the introduction and rapid acceptance of organosilicon, organoaluminum[1], and organic compounds of other non-transition metals as general and versatile reagents for the synthetic chemist. The value of these reagents lies in their ability to 1) render possible unique and otherwise unattainable transformations under mild conditions, 2) undergo a variety of modifications, and 3) afford the desired product in a selective or specific manner.

Although their role in the olefin oriented world of petrochemicals is well-established, organoaluminum reagents are relative newcomers as tools in selective organic syntheses. The characteristic properties of these reagents derive mainly from the high Lewis acidity of the organoaluminum monomers, which is directly related to the tendency of the aluminum atom to complete electron octets. Bonds from aluminum to electronegative atoms such as oxygen or the halogens are consequently strong: the energy of the Al—O bond is estimated to be 138 kcal/mol[2]. Indeed, nearly all alkylaluminum compounds react vigorously with oxygen or air. Trialkylaluminum compounds and dialkylaluminum halides are particularly reactive and often ignite spontaneously[3]. The strong Lewis acidity of organoaluminum compounds appears to account for their great tendency to form 1:1 complexes, even with neutral bases such as ethers. These properties (commonly identified with "oxygenophilicity") are of great value in the design of selective synthetic reactions. The coordination of a molecule invariably causes a change of reactivity, and the coordinated group may be activated or deactivated depending upon the type of reaction. Furthermore, on coordination of an organic molecule an auxiliary bond can become coupled to the reagent and promote the desired reaction. Our initial studies on the development of selective reactions utilizing these advantages of organoaluminum reagents are reviewed below.

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2. Oxirane and Oxetane Ring Cleavage

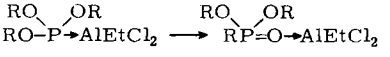
Organoaluminum compounds are strong Lewis acids and coordinate with neutral donor molecules to form stable complexes. Provided the bases do not bear acidic hydrogen atoms, the complexes can in most cases be distilled. The stability of 1:1 complexes with trialkylaluminum decreases in the sequence[4]:

$$Me_3N > Me_3P > Me_2O > Me_2S > Me_2Se > Me_2Te$$

Accordingly, it is possible to displace a weaker donor by one which is stronger[5],

$$Me_3PO + Me_3Al{\leftarrow}OEt_2 \longrightarrow Me_3Al{\leftarrow}OPMe_3 + Et_2O$$

In some complexes the coordinated Lewis acid undergoes rearrangement under relatively mild conditions. Thus, complexes of ethylaluminum dichloride with trimethyl or triethyl phosphites are thermally unstable and rearrange to the corresponding phosphonate complexes *(1)*[6].

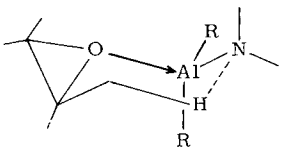


The formation of complexes with weakly basic ethers is reversible. With more strongly basic ethers, however, heating at sufficiently high temperature often brings about decomposition rather than dissociation to the original components of the complex. Depending upon the conditions and the substituents, oxirane derivatives are not only cleaved by many organoaluminum reagents but also undergo alkylation, reduction, or rearrangement[1].

The reaction of oxiranes with strong bases constitutes a well known synthetic method for the preparation of allyl alcohols. The method discovered by *Cope*[7], and further developed by *Crandall*[8] and *Rickborn*[9], involves isomerization with lithium diethylamide. Unfortunately, however, the proce-

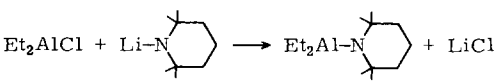
dure requires undesirably high reaction temperatures and is rather nonselective in the sense that a methyl group on the ring usually contributes the proton to be removed. Accordingly, the double bond of the resulting allyl alcohol is rarely located in the main chain.

Since the oxirane ring is readily opened by organoaluminum compounds and since such compounds can be easily modified in various ways, it was of special interest to search for new aluminum reagents which would be suitable for the above mentioned transformation. At elevated temperatures, a variety of oxirane derivatives are isomerized by diisobutylaluminum hydride or triisobutylaluminum[10]; however, the reaction pattern is rather similar to that with lithium diethylamide in boiling benzene. A "pure" concerted *syn*-elimination would be desirable for this rearrangement, for then it would proceed in high yields, yet under such mild conditions that it could also be used with complex and multifunctional substrates. Our method is based on the strategy of simultaneous activation of both the oxirane ring and the proton to be removed. This idea is illustrated for the specific case of activation of an oxirane with dialkylaluminum amide [cf. *(2)*]. The proton transfer from substrate to amide is clearly more favored than in the case of other classical reagents, and the electrostatic forces ought to facilitate smoother rearrangement to the allyl alcohol.



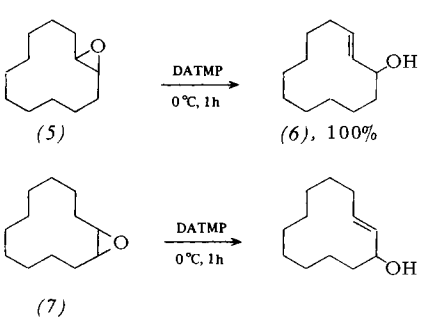
(2)

The realization of this rearrangement is in practice highly dependent upon the size of the substituents on the amide-nitrogen, since the enthalpy of formation of 1:1 complexes of aluminum amides with ethers is strongly influenced by the spatial bulkiness of these substituents[11]. A new organoaluminum reagent, diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP) *(4)*, is the reagent of choice and can be readily prepared from diethylaluminum chloride and the corresponding lithium amide *(3)*[12].



(3) DATMP *(4)*

Thus, on reaction with DATMP in benzene, (*E*)-cyclododecene oxide *(5)* is converted quantitatively within 1 h at 0 °C into (*E*)-2-cyclododecen-1-ol *(6)*. In contrast, under the same reaction conditions, the (*Z*)-isomer *(7)* afforded only 8% of the alcohol *(8)*. Treatment of a mixture of cyclopentene oxide, cyclohexene oxide, and cycloheptene oxide with DATMP at 0 °C merely resulted in the recovery of unchanged oxiranes. Thus, DATMP is virtually unreactive toward *cis*-2,3-disubstituted oxiranes.



(5) *(6)*, 100%

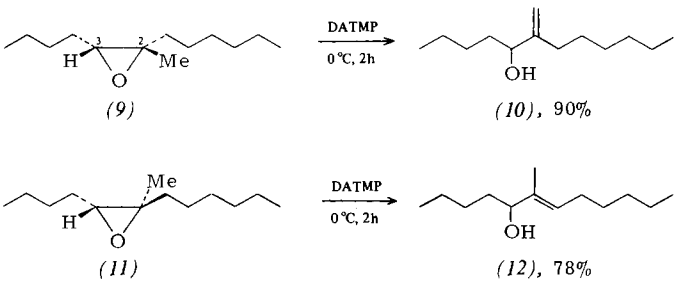
(7)

The reagent is very reactive toward 2,2,3-trisubstituted oxiranes such as *(9)* and *(11)*[12]. From observations the following selectivity rules can be derived:

Rule 1: The sole product is a secondary allyl alcohol.

Rule 2: The required proton is supplied by the alkyl group on C-2, which is located *cis* to the hydrogen atom on C-3.

Rule 3: The resulting double bond prefers the (*E*)-configuration.



(9) *(10)*, 90%

(11) *(12)*, 78%

The observed selectivity could be in keeping with a cyclic *syn*-elimination mechanism, in which ring opening is highly stereoelectronically demanding. As can be seen in Figure 1, the alternative approach of the organoaluminum compound from the side opposite to that of the hydrogen atom is strongly hindered by the alkyl groups R^2 and R^3. Hence, it can be concluded that the organoaluminum compound adds to the oxirane preferentially on the same side as hydrogen at C-3 ("steric approach control"). The favored direction of elimination is accounted for by the preferred abstraction of the hydrogen which enables a greater orbital overlap in the cyclic transi-

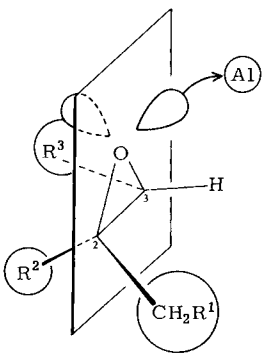


Fig. 1. Addition of an organoaluminum compound to an oxirane (selectivity rules 1 and 2).

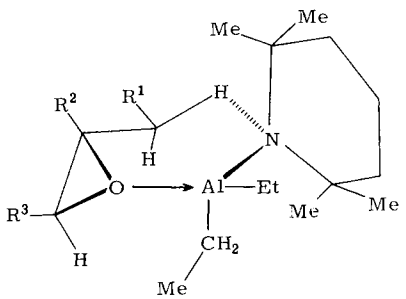
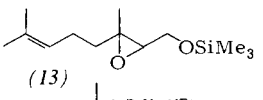


Fig. 2. Preferred conformation of an intermediary DATMP-oxirane complex (selectivity rule 3).

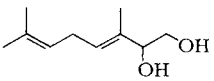
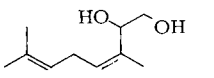
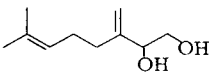
tion state. Figure 2 shows a view of the DATMP-oxirane complex in what appears to be the energetically most favorable conformation. This conformation is introduced with rigid stereochemical control by the indicated nonbonding interactions.

A considerable number of experimental findings are in accord with predictions based on the above speculations. One interesting example is the reaction of the trimethylsiloxymethyl-substituted oxirane *(13)*[13], obtained from geraniol. The yields of the diols *(14)*, *(15)* and *(16)* show dramatically that the selection rules 1 and 2 (Figure 1) are fulfilled by both DATMP and $(i\text{-Pr})_2$ N—$AlEt_2$, while selection rule 3 (Figure 2) is fulfilled only by DATMP. In contrast to *(13)*,

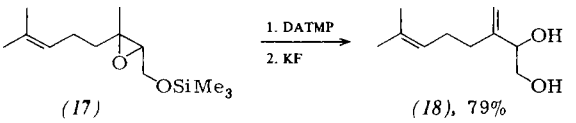


(13)

1. R_2N–$AlEt_2$
2. KF/MeOH

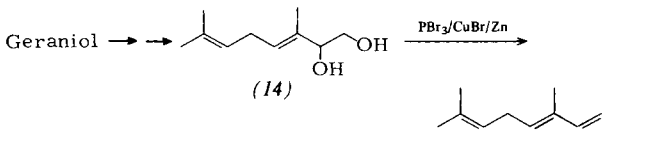
		DATMP	$(i\text{-Pr})_2N$–$AlEt_2$
	*(14)*	59%	28%
	*(15)*	<3%	31%
	*(16)*	<3%	<5%

reaction of the isomeric oxirane *(17)* (prepared from nerol) with DATMP/KF affords only the diol *(18)* having the double bond in the side-chain[13].



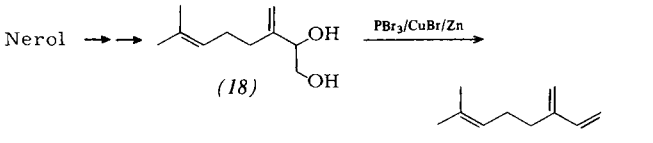
(17) *(18)*, 79%

In principle, removal of both hydroxy groups of the resulting 3-ene-1,2-diol systems should provide naturally occurring trienic monoterpenes—ocimene from *(14)* and myrcene from *(18)*. However, the reaction with DMF-acetal and acetic anhydride and other potential reactions did not proceed smoothly; success was eventually obtained with a new one-pot operation, which involves initial bromination with a mixture of cuprous bromide and phosphorus tribromide in ether followed by debromination with zinc powder[13].



(14)

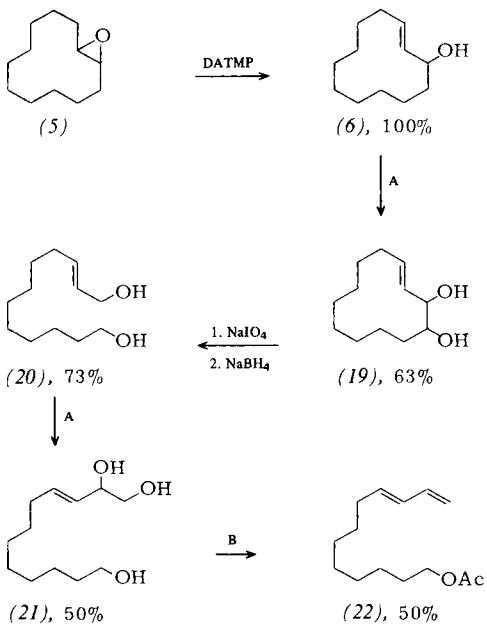
trans-β-Ocimene, 66%



(18)

Myrcene, 58%

Triple utilization of this reaction sequence enabled the synthesis of the ester *(22)* from the cyclododecene oxide *(5)*; *(22)* is the sex hormone of the red bollworm moth *Diparopsis castanea* Hmps.

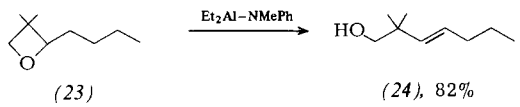


(5) *(6)*, 100% *(20)*, 73% *(19)*, 63% *(21)*, 50% *(22)*, 50%

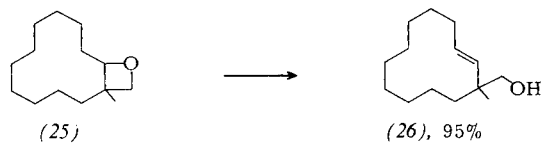
A: 1. *t*-BuOOH/$VO(acac)_2$; 2. Me_3SiCl; 3. DATMP; 4 KF

B: 1. $Me_2C(OMe)_2$; 2. Ac_2O; 3. $H^{\oplus}$; 4. PBr_3/CuBr/Zn

The enthalpy of formation for 1:1 complexes of organoaluminum compounds and oxiranes is probably greater than for the corresponding complexes with tetrahydrofuran and other cyclic ethers. The success of the DATMP promoted oxirane rearrangement may be attributed to this strong aluminum-ether coordination. As an extension of this work, it seemed logical to expect that four-membered oxetane rings might also be susceptible to the attack of aluminum amide and that a useful stereoselective route to homoallyl alcohols might thereby become available. This is indeed the case, as demonstrated by the reaction of 2-butyl-3,3-dimethyloxetane *(23)* with diethylaluminum methylanilide in boiling ben-



(23) *(24)*, 82%

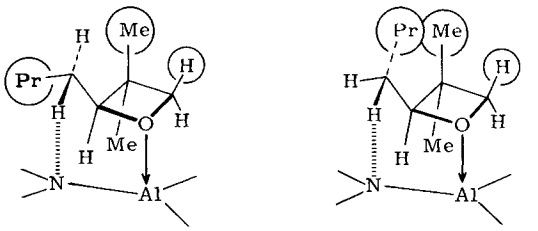


(25) *(26)*, 95%

zene—despite the higher reaction temperature and longer reaction time required, the (*E*)-homoallyl alcohol *(24)* is formed in high yields and is completely homogeneous (>99% purity)—as is also the cyclic homoallyl alcohol *(26)*[14].

The high stereoselectivity (>99%) in the synthesis of the homoallyl alcohols from oxetanes can be rationalized analo-

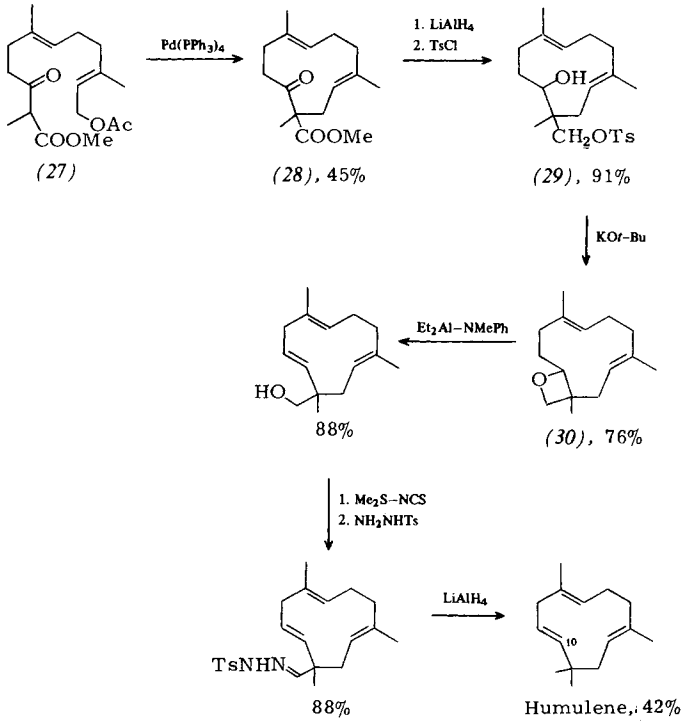
gously as in the aforementioned ring-opening of oxiranes to allyl alcohols. Thus, in the reaction with the oxetane *(23)*, the relative conformational energies of forms A and B should determine the product ratio (Fig. 3). The conformer A, which gives rise to the (*E*)-isomer *(24)*, appears to be favored in all respects; in the alternative structure B, severe nonbonded interactions develop between the *n*-propyl group and one of the methyl substituents of the oxetane ring which preclude formation of the (*Z*)-isomer of *(24)*.



A

Fig. 3. Two conformers of the complex from oxetane *(23)* and diethylaluminum methylanilide: A is strongly preferred over B.

With this methodology at hand, we could synthesize humulene, an important medium-ring sesquiterpene, in a highly stereoselective manner[14]. It should be pointed out that the protonation at C-10 can lead to a rather complicated rearrangement which will destroy the whole ring system.

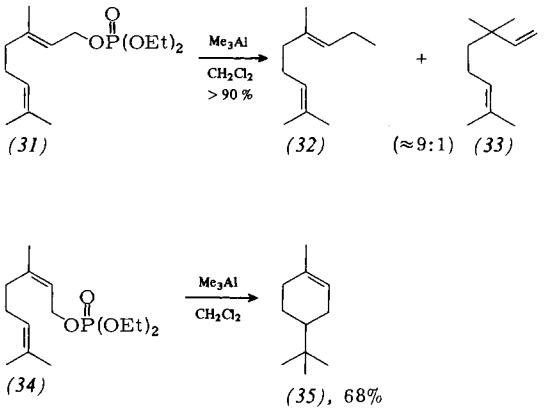


3. Heterolysis of Allyl Phosphates

Since formation of a 1:1 complex is evidently an essential step before oxirane or oxetane rearrangement, we have sought to extend the investigation to other systems which also have a high tendency to coordinate with organoaluminum compounds. Among these, allyl phosphates are of outstanding interest for the following reasons:

1. Trialkylaluminum-phosphane oxide adducts have exceedingly high enthalpies of formation (26–32 kcal/mol)[15], possibly because of the high polarity of the phosphorus-oxygen bond.

2. The considerable importance of phosphates in biological systems[16].



Reaction of diethyl(geranyl) phosphate *(31)* with trimethylaluminum in dichloromethane under argon leads stereospecifically to the isomeric dienes *(32)* and *(33)* in >90% yield[17]. A dramatic alteration in the course of the reaction occurs when the reaction is carried out with diethyl(neryl) phosphate as starting material. Although limonene and terpinolene are formed, the major product is the cyclohexene derivative *(35)*[17].

These striking observations demonstrate that either intermediary allylic carbocations strictly preserve their steric integrities in such transformations, or that a purely concerted mechanism is operative in the whole process.

In view of the efficiency of the mild and stereospecific heterolysis of allyl phosphates by trialkylaluminum compounds, the behavior of certain reagents of type R_2AlX (X = SR, NHR, or OR) has been studied systematically[17]. Treatment of geranyl or neryl phosphates in hexane with these aluminum reagents leads to regio- and stereospecific formation of substitution products. Examples illustrating the synthesis of sulfides, amines, and ethers in this way are cited in Table 1. It is important to note that both phosphates attack organoaluminum amides, alkoxides, and sulfides preferentially at the Al—N, Al—O, and Al—S bonds, respectively, leaving the C—Al bond intact. A similar effect has been observed in the protolytic cleavage of the Al—N bond[18]:

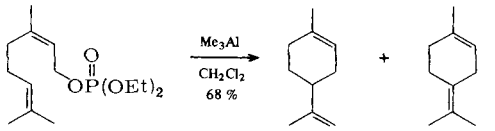
$$Et_2AlNH_2 + MeOH \longrightarrow Et_2AlOMe + NH_3$$

Table 1. Reaction of diethyl(geranyl)phosphate *(31)* and diethyl(neryl) phosphate *(34)* with 4 equivalents Me_2AlX in hexane. Yield = yield of isolated product.

RMeC=CHCH$_2$—OP(O)(OEt)$_2$ $\xrightarrow{Me_2AlX}$ RMeC=CHCH$_2$—X
(31), (34)

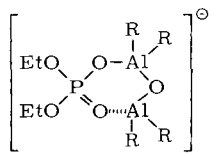
Substrate RMeC=CHCH$_2$ =	Reaction Conditions t[h]/T[°C]	X	Yield (%)
Geranyl	0.5/0	S-*tert*-Bu	97
Neryl	0.5/0	S-*tert*-Bu	92
Neryl	0.5/0	SPh	83
Geranyl	0.5/0; 12/20	NHPh	74
Neryl	0.5/0; 12/20	NHPh	82
Geranyl	0.3/0; 1.5/20	OPh	85
Neryl	1/0; 1/20	OPh	77

With the practical problem of selective heterolysis of allyl phosphates having been solved, we concerned ourselves next with biomimetic processes for the conversion of acyclic terpene derivatives into cyclic compounds. It was soon realized that aluminum compounds serve as useful reagents for such allylcation promoted cyclization reactions. The concept was first tested with a simple acyclic monoterpene, diethyl(neryl)phosphate *(34)*. In the presence of organoaluminum compounds of type R_2AlX (X = NHR or OR), and using dichloromethane as solvent, facile cyclization to limonene and terpinolene took place[17].



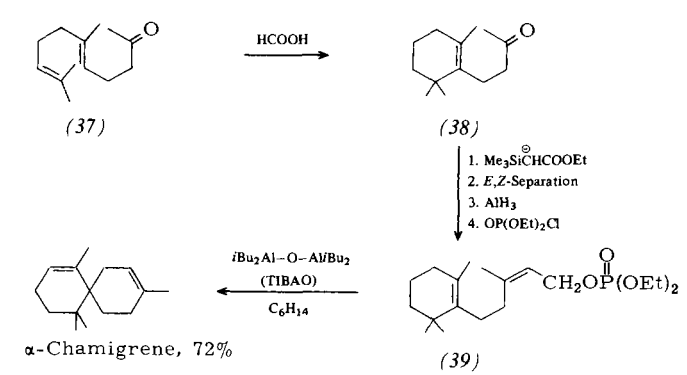
(34) Limonene Terpinolene

The pronounced effect of solvent on the course of reaction (compare with Table 1) must be related in part to the nature of the ion pair involved in the key step of the reaction. In nonpolar solvents a tight ion pair might be involved, though the possibility of a concerted process being operative has not yet been ruled out. In more polar solvents, however, the ion pair could be more widely separated and the cationic cyclization take place rather easily. Indeed, some solvation of trialkylaluminum by dichloromethane has been reported[19].



(36), R = *i*-Bu

It seemed logical to expect that much more stable counter ions might play a significant role in this kind of reaction. For preparing the cyclized products more selectively, we thus examined the behavior of tetraisobutyldialuminoxane, (TIBAO), which is readily obtained by the action of 0.5 equivalents of water on diisobutylaluminum hydride in THF followed by concentration *in vacuo*. It is assumed that the phosphate and TIBAO form a stable anionic chelate complex *(36)* containing a puckered six-membered ring. Reaction of the neryl ester *(34)* with excess TIBAO in dichloromethane (1 h at 0 °C and 3 h at 20 °C) afforded limonene and terpinolene in good yields[17]. The cyclization with TIBAO is not significantly affected by the solvent; in hexane or tetrahydrofuran the yields are 54 and 80% respectively[17]. A simple total synthesis of α-chamigrene has been successfully carried out with this powerful cyclization reagent[17].



(37) *(38)* *(39)* α-Chamigrene, 72%

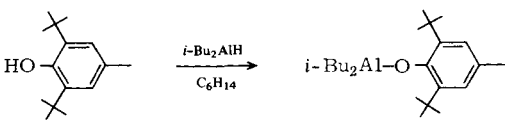
So far, we have ignored the product selectivity in the cyclization of the dienes. Treatment of the neryl ester *(34)* with TIBAO in various solvent systems indeed affords limonene and terpinolene uncontaminated with acyclic hydrocarbons, but the observed limonene/terpinolene ratio strongly depends upon the nature of the solvent. In tetrahydrofuran, this ratio is as low as 63:37 (Table 2)[17]. Moderate selectivities have been achieved in less polar media; this must be due in part to a synchronized process, as is operative in nonpolar solvents.

Table 2. Relative yields of limonene and terpinolene in the reaction of diethyl(neryl) phosphate *(34)* with various organoaluminum compounds in different solvents.

Reagent	Solvent	Limonene/Terpinolene
TIBAO [a]	Hexane	89:11
TIBAO [a]	CH_2Cl_2	88:12
Me_2AlOPh	CH_2Cl_2	86:14
$(Me_2Al)_2NPh$	CH_2Cl_2	80:20
$Me_2AlNHPh$	CH_2Cl_2	79:21
TIBAO [a]	THF	63:37

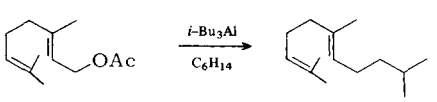
[a] Tetraisobutyldialuminoxane.

Terpinolene must have originated from a sequence featuring discrete molecular species with carbocationic character (terpinyl cations) as produced in polar solvents. Unfortunately, however, treatment of allyl phosphates in hexane with aluminum alkoxides or amides usually results in formation of substitution products rather than cyclic dienes (cf. Table 1). We therefore, turned our attention to organoaluminum compounds containing organic groups sufficiently bulky for preventing such substitution reactions. The most satisfactory reagent proved to be diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide *(40)*[20]. Presence of the large alkyl substituents in the *ortho* position appears to be highly favorable for the present purpose because of significant frontal steric hindrance. When the neryl ester *(34)* was treated with this bulky aluminum reagent *(40)* in hexane at −78 °C, limonene was produced almost exclusively. Analysis of the crude product by GLPC showed it to contain 99% limonene and 1% terpinolene[20].



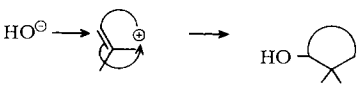
(40)

Since organoaluminum compounds form rather stable 1:1 complexes with esters[21], the reactions of allyl esters of acetic, formic, and carbonic acids were examined in detail. On the basis of the results obtained thus far, the reactions of these derivatives, e.g. *(41)*, qualify as important additions to the reactions of allyl phosphates. The hydrocarbon *(42)* is formed with 97% purity[22].

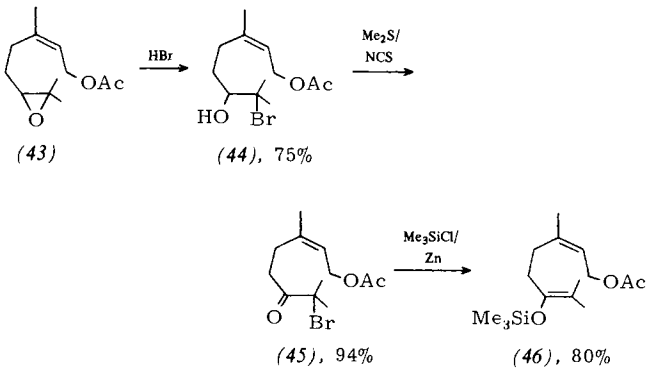


(41) *(42)*, 66%

The cyclization of neryl phosphate *(34)* leads to six-membered rings. If the more stable tertiary cationic center could be utilized, seven-membered rings would result. Since the *anti*-Markovnikov cyclization widely occurs in natural products—the most noteworthy being the enzymic formation of karahanaenone, humulene, and lanosterol (C-ring)—it was of special importance to search for systems which give *anti*-Markovnikov ring closure in biomimetic processes. It seemed reasonable to examine the behavior of silyl enol ethers as nucleophilic participants in terpene cyclizations, since a silyl enol ether ideally located in space for interaction with a developing cationic center should cyclize in a regiospecific manner.

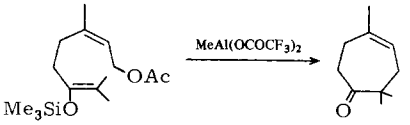


Since the neryl ester *(34)* has been shown to undergo facile organoaluminum-promoted cyclization to give limonene in good yields[17], we decided to examine the cyclization of the closely related enol ether *(46)* using several different organoaluminum reagents. Thus, upon treatment with methylaluminum bis(trifluoroacetate) in dichloromethane (10 min at 0°C and 3 h at 25°C) we obtained karahanaenone in 95% yield[23]. Reaction of *(46)* with trimethylaluminum resulted



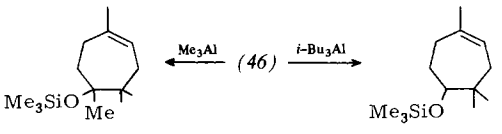
(43) *(44)*, 75% *(45)*, 94% *(46)*, 80%

in formation of the *C*-methylated cyclic silyl ether *(47)*. In contrast, when it was treated with triisobutylaluminum in



(46) Karahanaenone, 95%

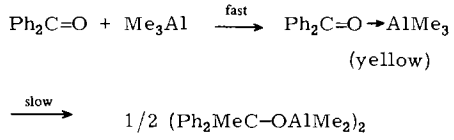
hexane, a dramatic alteration in the course of the reaction occurred: the predominant product was the silyl ether *(48)*, resulting from the unprecedented reductive cyclization.



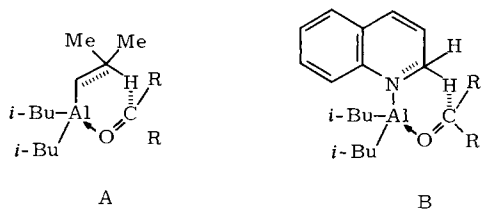
(47), 76% *(48)*, 71%

4. Reactions with Carbonyl Compounds

While the overall mode of reaction of trialkylaluminum reagents with carbonyl compounds parallels the reactions known for Grignard reagents, there are nevertheless significant differences. Thus, reaction of trialkylaluminum with a ketone (molar ratio 1:1) gives a long-lived monomeric 1:1 complex which very slowly decomposes unimolecularly to dimeric dialkylaluminum alkoxide[24]. The use of organoaluminum compounds in this sector has not yet been thoroughly investigated and it is probable that novel reactions will be found which have no parallel in the chemistry of the commonly used Grignard reagents.

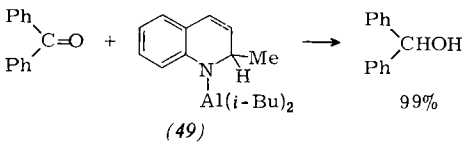


Hydride transfer from triisobutylaluminum to the carbonyl carbon occurs preferentially or exclusively from the less hindered side of the molecule. This remarkable steric approach control is ascribed to rate-determining decomposition of the ketone-triisobutylaluminum complex through the cyclic transition state A (Fig. 4)[25]. On the basis of this mechanism, we examined the reduction of ketones with organoaluminum compounds containing bulky groups, one of which was diisobutylaluminum 1,2-dihydroquinaldide *(49)*, which can be readily prepared from quinaldine and diisobutylaluminum hydride[26,27].



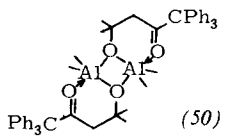
A B

Fig. 4. Cyclic transition state of the reaction of ketones with triisobutyllithium (A) and diisobutylaluminum 1,2-dihydroquinaldide *(49)* (B).



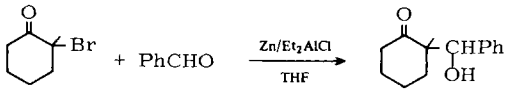
(49)

For complexes of organoaluminum compounds and ketones yet another mode of reaction is possible. Ketones which can undergo enolization under the influence of organoaluminum compounds may then condense with further ketone. Hence condensation may compete with alkylation and reduction. The intermediary dimeric aluminum β-oxoenolate of type *(50)* is rather stable and in some cases could be isolated in pure crystalline form[28]. In principle, therefore, organoaluminum compound have vast potential as reagents for aldol-type condensations. However, this concept has not been generally accepted in preparative chemistry owing to the lack of a suitable method for converting a carbonyl compound into a reactive aluminum enolate.



(50)

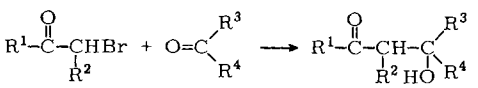
With the aim of circumventing these limitations and utilizing the unique features of organoaluminum compounds more effectively, we are currently investigating aldol-type reactions promoted by aluminum reagents in the presence of zinc dust. An example is the reaction of ketone *(51)* with benzaldehyde[29]. The critical part of the process is the coupled attack



(51) *(52)*, 100%

on the α-haloketone by dialkylaluminum chloride and zinc dust which generates an aluminum enolate regioselectively. The reduction of the α-haloketone to enolate is clearly more favorable than the simple Reformatsky reaction. The aluminum enolate thus generated is sufficiently reactive to add to the carbonyl compounds present in the system. β-Oxoenolates are formed which, after workup yield the β-hydroxycarbonyl compounds. The reaction of two molecules of an α-haloketone with each other can be prevented if α-haloketone and carbonyl compound are simultaneously added to the organoaluminum compound at low temperature—provided the reduction proceeds sufficiently fast under acceptable conditions. In fact, the reaction of α-haloketones with a series of carbonyl derivatives is found to be a useful regioselective route to β-hydroxycarbonyl derivatives (Table 3)[29].

Table 3. Examples of β-hydroxycarbonyl compounds synthesized from α-bromocarbonyl compounds and aldehydes or ketones with zinc and diethylaluminum chloride (in anhydrous THF).



R^1	R^2	R^3	R^4	T[°C]	Yield [%]
—$(CH_2)_4$—		Ph	H	−20	97
		i-Pr	H	−20	93
Ph	H	Ph	H	−20	95
		i-Pr	H	−20	92
		—$(CH_2)_5$—		−20	83
EtO	H	Ph	H	0	94

5. Closing Remarks

It was not the purpose of this progress report to consider all the known aluminum-promoted reactions individually but rather to present several new selective reactions based on the formation of 1:1 complexes of organoaluminum compounds with neutral Lewis bases. The selectivity is largely due to the presence of a coordinating group of the substrate which enables an adjacent functional group to react intramolecularly with a ligand of the aluminum. Thus, organoaluminum compounds effect selective functionalization using the principles, which to a very crude approximation, Nature incorporates in her enzymic processes. Even in our simple examples the selectivities achieved suggest that organoaluminum compounds have an important role to play in the synthetic methods of the future.

Special thanks are due to our able collaborators who have made many significant contributions to the planning of this research endeavor: Shin Tanaka, Arata Yasuda (Section 2), Yoshizo Kitagawa, Shinsuke Hashimoto, Satoshi Iemura, Akira Itoh, and Keiji Maruoka (Section 3 and 4). Financial support from the Ministry of Education, Japanese Gouvernment (Grants No. 911502, 011010, 110309, 203014, 247077), is gratefully acknowledged.

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Production and Utilization of Amino Acids

By Yoshiharu Izumi, Ichiro Chibata, and Tamio Itoh[*]

The amino acid industry has been steadily expanding since monosodium glutamate was first marketed as a flavoring material in 1909. Its production has recently reached almost the 1 billion dollar level. Amino acids are produced by extraction from protein hydrolyzates, by fermentation with the aid of microorganisms, by enzymatic processes, and by chemical synthesis. To obtain natural L-amino acid, chemical synthesis generally requires two additional steps, *i.e.* optical resolution and racemization of the D isomer. The most important applications of amino acids include the fortification of plant food and feeds by supplementation of the deficient essential amino acid(s). Apart from their uses in the food industry, medical applications of amino acids (nutritional preparations and therapeutic agents) are becoming increasingly important.

1. Introduction

More than one hundred years ago, *Ritthausen* was engaged in the isolation of amino acids from gluten hydrolyzates at Königsberg. In 1866, he sent a specimen of crystalline glutamic acid to the mineralogist *Werther*, stating in an accompanying letter: "Dieselbe schmeckt deutlich sauer, etwas adstringend, erinnert aber im Nachgeschmack entfernt an concentrirten Fleischextract"[1]. However, use of glutamic acid as a flavoring material was not developed further in Germany. In 1908, the Japanese scientist *Ikeda* discovered that L-glutamic acid was the essential component of sea-tangle extracts, traditional Japanese soup stocks. Within a year, monosodium L-glutamate came onto the market as a culinary flavoring material. Since then the amino acid industry has continued to develop, with Japan retaining world leadership in this field.

All the amino acids occurring in proteins are now produced industrially. The total annual output of amino acids has a value of about $ 1000 million, and is still increasing. Table 1 summarizes the production methods, the output, and the approximate price of each amino acid.

The proteins essential for life are made up of about twenty kinds of amino acids. These amphoteric compounds contain at least one amino group and a carboxy group. Because of their characteristic properties, the applications of amino acids include such diverse fields as additives to foods and animal feeds, medical products, cosmetics, synthetic polymers, detergents, *etc.*

In 1974, the present authors published a book on the chemical synthesis and utilization of amino acids[2]. Another comprehensive book has also been published on microbial production of amino acids[3]. The present review mainly discusses recent advances in the industrial production and applications of amino acids.

Table 1. Survey of amino acid production (1977).

Amino acid	Method of production [a]	Quantity [t/a]	Price range [b]
L-Alanine	E	50–100	IV
L-Arginine(·HCl)	F, Ex	200–300	III
L-Asparagine	S	10–50	II
L-Aspartic acid	E	500–1000	II
L-Cysteine	S	50–100	III
L-Cystine	Ex	10–50	III
L-(2,4-Dihydroxyphenyl)alanine	S	100–200	II
L-Glutamine	F	200–300	III
L-Glutamic acid(Na)	F	250000	I
Glycine	S	3000	I
L-Histidine(·HCl)	F, Ex	50–100	V
L-Hydroxyproline	Ex	10–50	V
L-Isoleucine	F	10–50	V
L-Leucine	Ex	50–100	III
L-Lysine(·HCl)	F	25000	II
L-Methionine	S	50–100	III
DL-Methionine	S	100000	II
L-Phenylalanine	S	50–100	IV
L-Proline	F	50–100	V
L-Serine	E, S	10–50	IV
L-Threonine	F, S	50–100	IV
L-Tryptophan	S	50–100	V
L-Tyrosine	Ex	10–50	III
L-Valine	S, F	50–100	III

[a] Method of production: E, enzymatic; Ex, extractive; F, fermentative; S, synthetic.

[b] Price range: I, <4 $/kg; II, 4–20 $/kg; III, 20–40 $/kg; IV, 40–80 $/kg; V, >80 $/kg.

2. Production of Amino Acids

The history of amino acid production is typified by that of monosodium glutamate (MSG). In the first commercial production process for MSG in 1909, L-glutamic acid was separated as hydrochloride from wheat gluten hydrolyzed with hydrochloric acid. Production of MSG by isolation from protein hydrolyzate continued for some 50 years. In 1955, the microbial production of L-glutamic acid from simple materials such as glucose and ammonia was developed in Japan. Since then, this fermentation method has been applied to the production of a variety of amino acids. At the same time, methods of synthesis and optical resolution were also studied, and the synthetic production of glutamic acid could be launched in 1960. Meanwhile, other amino acids such as DL-methionine, glycine, and L-tryptophan are also manufactured in this way.

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Amino acids can be produced by extraction from protein hydrolyzate, chemical synthesis, and microbial production. Enzymatic methods, such as production of L-aspartic acid from fumaric acid by aspartase and production of L-alanine from L-aspartic acid by aspartic-β-decarboxylase, have also been performed industrially. Further, continuous processes for enzymatic optical resolution and enzymatic synthesis have been developed using immobilized enzymes and immobilized microbial cells.

Most of the above mentioned techniques for the industrial production of amino acids were developed and introduced on an industrial scale in Japan. With the introduction of these production techniques, it became possible to produce economically various kinds of pure, optically active amino acids. As a result, the practical application of amino acids in various fields has been increasing year by year and has now become a viable branch of industry, which could be called the "amino acid industry".

2.1 Extraction Method

A certain amino acid can be separated from a protein hydrolyzate if its properties differ significantly from those of other amino acids present in the hydrolyzate. For instance, a cystine and tyrosine rich fraction can be readily separated from protein hydrolyzate by removing the fraction of water soluble amino acids, since cystine and tyrosine are sparingly soluble in water. Even today, cystine and tyrosine are still commercially produced by this simple separation method. Hydroxyproline is also produced by extraction (from gelatine hydrolyzate). The conventional separation method for production of arginine and histidine is now being replaced by microbial production.

2.2 Fermentation Method

The development of the fermentation method for production of amino acids, such as glutamic acid, began with screening programs for wild type microorganisms which could accumulate amino acids, given suitable media and cultural conditions. However, the kind of amino acid was limited and concentrations were low. Only on introduction of the methods of modern genetic biochemistry did it become possible to produce most amino acids by fermentation.

2.2.1. Use of Wild-Type Microorganisms

As a typical example, microbial production of L-glutamic acid will now be described.

In microorganisms, glutamic acid is formed by condensation of ammonia with α-oxoglutaric acid which in turn is formed from glucose *via* pyruvic acid (Fig. 1). Generally, microorganisms produce glutamic acid at just the level necessary to maintain life and growth. Certain microorganisms such as *Corynebacterium glutamicum* and *Brevibacterium flavum* have a very active enzyme system producing glutamic acid and excrete the amino acid from the cell. Since the first isolation of microorganism showing high glutamic acid productivity in 1955, the fermentation technique has greatly improved Nowadays, as much as 500 kg of L-glutamic acid can be

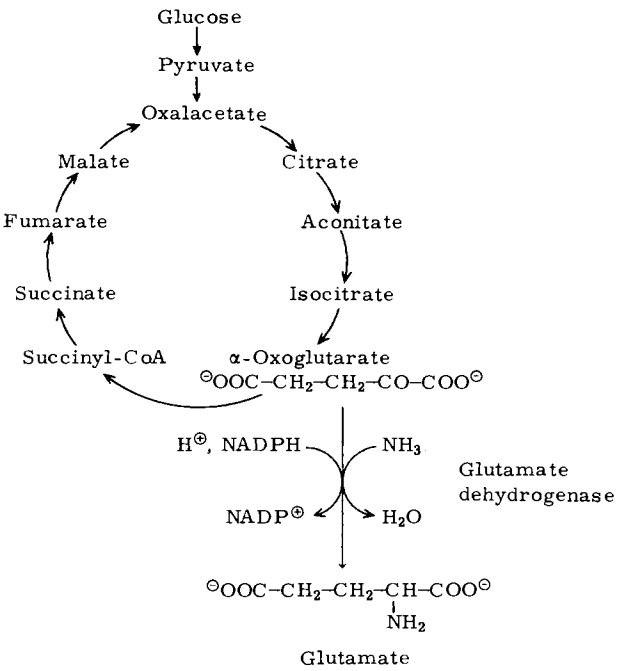


Fig. 1. Biosynthesis of glutamate.

produced from 1 tonne of glucose. The less expensive carbon sources beet and cane molasses are used instead of glucose in the fermentation medium. Furthermore, acetic acid, ethanol, and *n*-paraffins are also utilizable for this purpose.

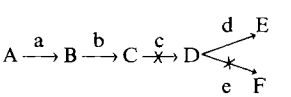
Fermentation is carried out as follows. To a sterilized tank (fermenter) are added an aqueous solution of carbon source as well as vitamins and minerals required for growth. After inoculation with a microorganism producing glutamic acid, air and ammonia are supplied to the vigorously stirred culture medium. The temperature is maintained at about 35 °C during this fermentation. After approximately 40 hours' culture, a large amount of glutamic acid has accumulated in the culture broth.

When the direct fermentative production of amino acids from sugar is difficult, appropriate intermediates are used. For example, isoleucine[4] and serine[5] are produced by fermentation in media containing D-threonine and glycine, respectively.

2.2.2. Use of Mutants

As stated in Section 2.2.1, only a limited number of amino acids can be produced by fermentation with wild-type microorganisms, since formation of amino acids is generally controlled by feedback mechanisms in microorganisms. This drawback can be overcome by using mutants accumulating an excess of specified amino acids. Several methods have been developed, as described below.

Use of auxotrophic mutants: Auxotrophic mutants, which lack one or more enzymes required for biosynthesis of an amino acid, can be used for microbial production of amino acids. The principle of the method is as follows: 1) amino



acid D-less mutant (the mutant requires amino acid D for growth) accumulates amino acid C owing to lack of enzyme c; 2) amino acid F-less mutant lacking enzyme e can be used for accumulation of amino acid E on another branched pathway.

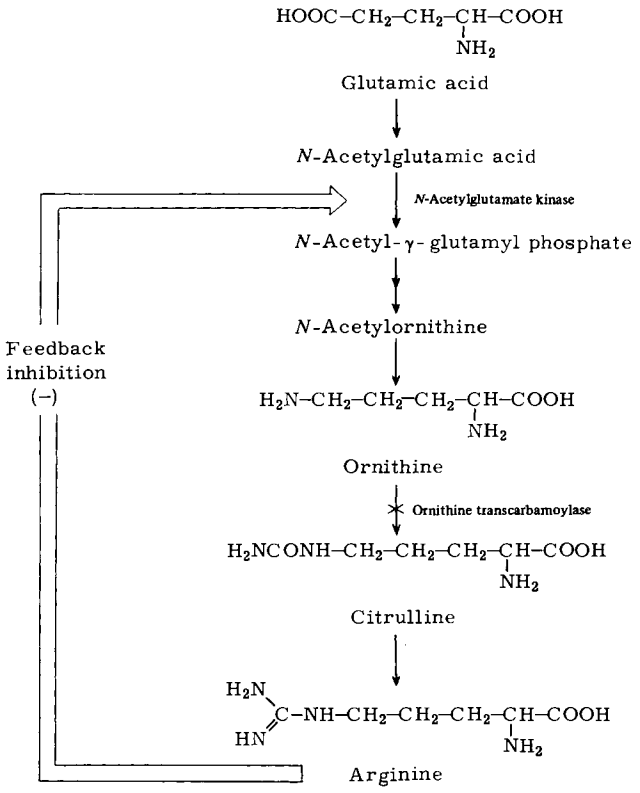


Fig. 2. Ornithine accumulation by a citrulline-deficient mutant of *Corynebacterium glutamicum*.

As shown in Figure 2, an example of the former case is the accumulation of ornithine by a citrulline-less mutant of *Corynebacterium glutamicum* which lacks ornithine carbamoyl transferase[6]. An example of the latter case is the accumulation of lysine by homoserine-less mutants of *Corynebacterium glutamicum* and *Escherichia coli*[7]. In these mutants, the lack of homoserine dehydrogenase blocks the pathway from aspartic semialdehyde to homoserine, leading to accumulation of lysine, the end product of a branched pathway. Other typical examples of the use of auxotrophic mutants are shown in Table 2.

Table 2. Accumulation of amino acid by auxotrophic mutants.

Product	Required amino acid	Microorganism	Ref.
Ornithine	citrulline	*Corynebacterium glutamicum*	[6]
Lysine	homoserine (threonine + methionine)	*Corynebacterium glutamicum*	[7]
Citrulline	arginine	*Bacillus subtilis*	[8]
Valine	leucine	*Corynebacterium glutamicum*	[9]
Threonine	methionine + isoleucine + diaminopimelic acid	*Escherichia coli*	[10]

Use of regulatory mutants: Growth of microorganisms can be inhibited by certain amino acid analogs. However, some microorganisms become resistant to these compounds by mutation. In these mutants, feedback control is lost and accumulation of excess amino acid occurs. These mutants are called regulatory mutants; some examples of the production of amino acids with their aid are shown in Table 3. Besides the above simple mutants, the use of polyauxotrophic mutants and auxotrophic regulatory mutants is steadily increasing[17].

Table 3. Accumulation of amino acids by regulatory mutants.

Product	Amino acid analog	Microorganism	Ref.
Arginine	2-thiazolealanine	*Brevibacterium flavum*	[11]
Methionine	ethionine + selenomethionine + methionine hydroxamate	*Corynebacterium glutamicum*	[12]
Isoleucine	isoleucine-hydroxamate	*Serratia marcescens*	[13]
Isoleucine	α-amino-β-hydroxyvaleric acid + *O*-methylthreonine	*Brevibacterium flavum*	[14]
Tryptophan	5-fluorotryptophan + tryptophan-hydroxamate	*Corynebacterium glutamicum*	[15]
Lysine	*S*-(2-aminoethyl)-L-cysteine	*Brevibacterium flavum*	[16]

2.3. Enzymatic Method

In the fermentation method amino acids are produced by use of the entire enzyme function of microorganisms. Using only part of this function, some amino acids can be produced from suitable intermediates by microbial enzymes.

For instance, the following reaction producing L-aspartic acid can be carried out with a cell suspension of *Escherichia coli* (Fig. 3). The reaction is catalyzed by the action of aspartase in microbial cells[18]. The resulting L-aspartic acid yields L-alanine on an industrial scale by the action of L-aspartate β-decarboxylase of *Pseudomonas dacunhae* cells[19].

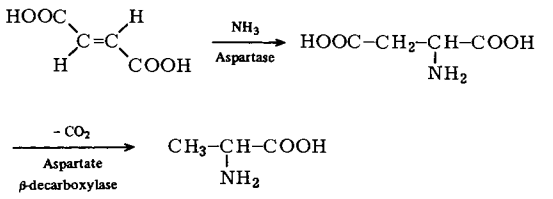


Fig. 3. Enzymatic formation of alanine from fumaric acid *via* aspartic acid.

With the aim of carrying out such enzyme reactions continuously, a technique has recently been developed for immobilization of microbial cells having high enzyme activity by entrapping into polymeric matrices[20]. Thus, L-aspartic acid is continuously produced in Japan using columns packed with immobilized microbial cells. This is the very first industrial application of an immobilized microbial cell system.

In the enzymatic synthesis of tryptophan from indole and pyruvate with tryptophanase, inosine is added to the reaction mixture to precipitate the resulting tryptophan as an insoluble tryptophan-inosine complex[21]. In this way tryptophan syn-

thesis is ensured. This is an interesting example of the application of reversible enzyme reactions.

An interesting enzymatic process for the production of L-lysine has been developed recently[22]. DL-α-aminocaprolactam is synthesized from cyclohexene, a by-product in the synthesis of caprolactam. Microbial L-aminocaprolactam hydrolase and aminocaprolactam racemase are simultaneously added to D,L-α-aminocaprolactam, resulting in its complete one-step enzymatic conversion into L-lysine as shown in Figure 4. Industrial application of this process is in progress; its economic competition with the recently developed microbial production of L-lysine seems very interesting.

Generally, enzymatic processes can be operated at higher concentrations and isolation of the products is also more simple than in the fermentation method. Therefore, the enzymatic method is advantageous when low-cost precursors are available and the reaction has a negative free energy.

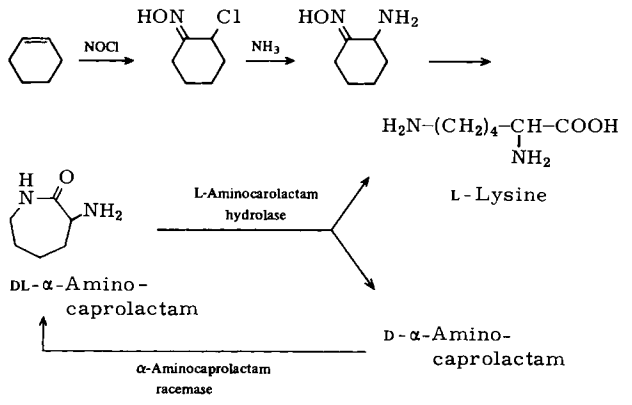


Fig. 4. Conversion of DL-aminocaprolactam into L-lysine.

This kind of interdisciplinary field between synthetic chemistry and biochemistry is a promising field for amino acid production.

2.4. Synthetic Method

Compared with the fermentation method, the synthetic technique can utilize a much greater variety of raw materials and processes. Furthermore, development of the chemical industry and technology promotes supplies of various materials at low cost and increases the competitive power of synthetic methods. For example, development of the petrochemical industry permitted large scale low-cost production of acrolein from propylene. This in turn made the synthetic production of methionine from acrolein economically feasible. However, the synthetic method requires a variety of raw materials produced by a highly developed chemical industry. This approach is therefore quite different from the fermentation method, which has no such limitations.

As described in Section 3, most applications exist for L-amino acids. Production of L-amino acids requires a combination of processes consisting of chemical synthesis, optical resolution and racemization of the D-amino acids. The two extra processes represent an economic disadvantage of the synthetic method. However, these demerits do not apply to glycine and methionine, because glycine has no asymmetric carbon and D- and L-methionines have almost equal nutritional value.

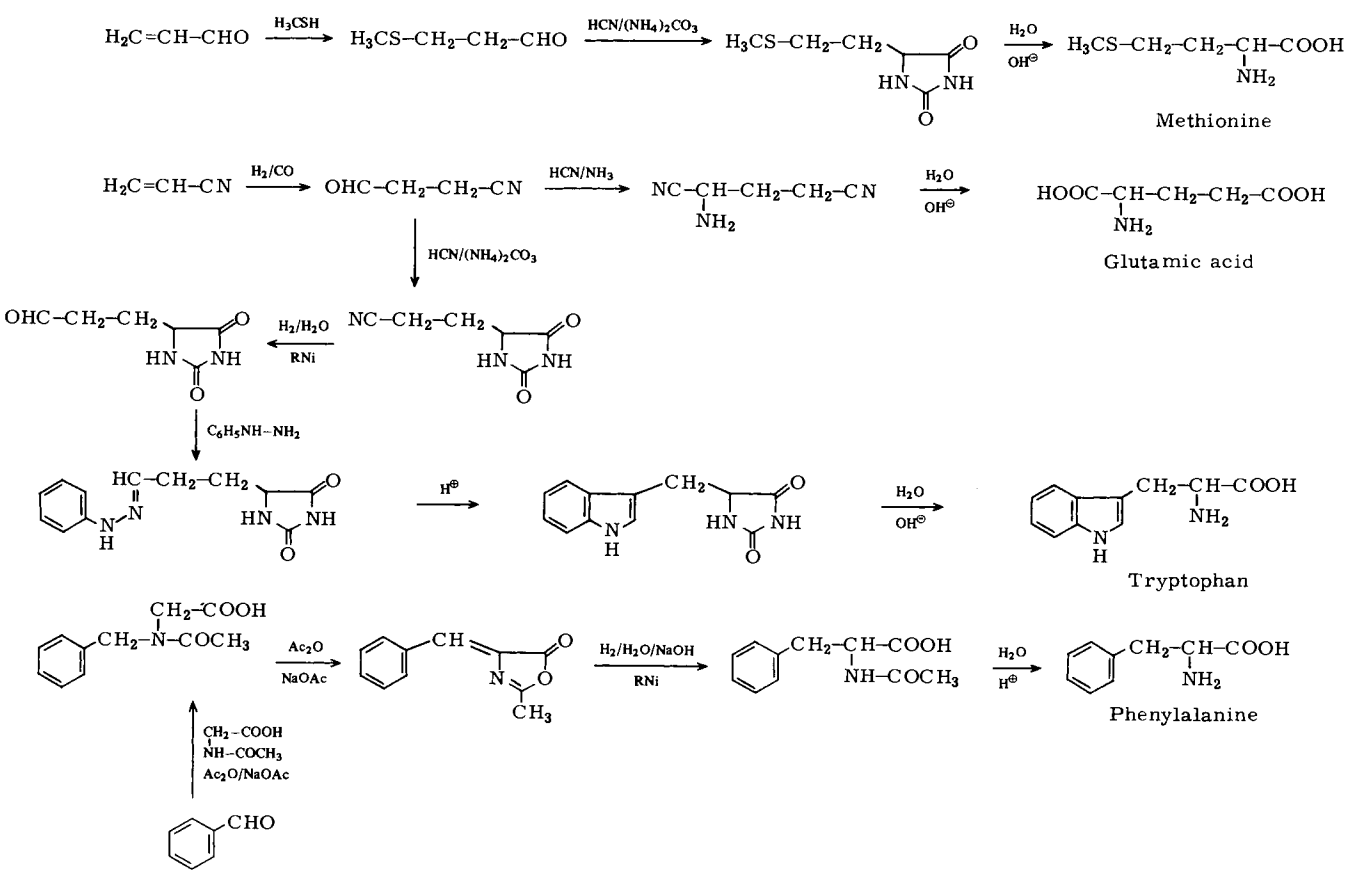


Fig. 5. Synthetic routes for some amino acids.

The industrial production of amino acids requires synthetic methods giving high yields. The Strecker method and the Snyder method meet the above requirements, and they both play a fundamental role in industrial production by chemical synthesis.

No practical fermentative methods have been developed for phenylalanine and tryptophan. These amino acids are therefore produced synthetically (Fig. 5); the value of this production method will be maintained over the near future. In spite of the disadvantages of synthetic methods, glutamic acid was synthesized on an industrial scale (Fig. 5) in Japan. Although the method was said to be competitive with the fermentative process, it has now been discontinued. The process for synthesis of methionine is also shown in Figure 5.

2.5. Optical Resolution

Optically active amino acids are obtained from synthetic DL-amino acids by optical resolution. Two techniques, *i.e.* the preferential crystallization procedure and the enzymatic procedure, are now employed. The former is based on preferential crystallization of the desired optically active isomer from a supersaturated solution of racemic amino acid on seeding with a small amount of the respective isomer. This procedure has been used for the resolution of glutamic acid and threonine. However, only few free amino acids can be resolved directly by this technique. In some instances, optical resolution of DL-amino acids becomes possible after conversion into appropriate salts or derivatives. One such example is the resolution of the ammonium salts of acylated tryptophan and acylated phenylalanine. Derivatives of aromatic sulfonic acids can also be resolved in this way, *e.g.* the sulfanilate of DL-lysine[23], the *m*-xylenesulfonate of DL-serine[24], and the anthraquinone-β-sulfonate of DL-lysine[25]. More recently, *N*-acyl-DL-proline[26] and DL-3-(3,4-methylenedioxyphenyl)-2-methylalaninehydrochloride[27] have also been resolved.

Although several methods are known for enzymatic resolution of DL-amino acids, the asymmetric hydrolysis of acyl-DL-amino acids by microbial aminoacylase is the only technique to have been adopted on an industrial scale. The method presently employed for the production of L-phenylalanine, L-tryptophan, L-valine, L-methionine, and L-2,4-dihydroxyphenylalanine (dopa) can be further improved by the use of immobilized enzyme systems. The aminoacylase is immobilized by ionic binding to a DEAE Sephadex support. The enzyme reaction is carried out continuously and automatically in columns packed with immobilized aminoacylase. This continuous production of optically active amino acids was developed in Japan and has been operated industrially since 1969. The flowsheet of the process is shown in Figure 6. Enzyme, substrate, and labor costs are low, and total production costs are more than 40% lower than for a conventional batch process using soluble enzyme.

2.6. Racemization

It is relatively easy to racemize optically active amino acids. Industrially, this is accomplished by heating aqueous solutions of amino acids or their salts at 150 to 250°C under pressure. *N*-Acetylamino acids are readily racemized at room

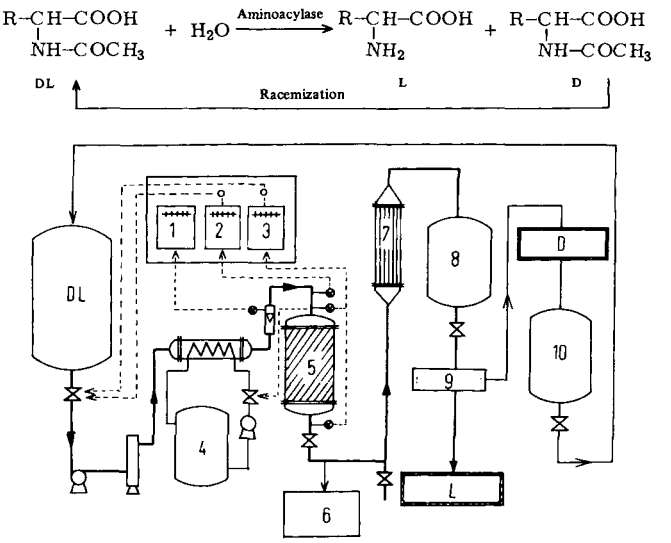


Fig. 6. Flow diagram for continuous production of L-amino acid by immobilized amino-acylase. DL, acetyl-DL-amino acid; L, L-amino acid; D, acetyl-D-amino acid; 1 to 3, measurement of flow rate, pH, and temperature; 4, hot water tank; 5, column containing immobilized amino-acylase; 6, automatic reaction recorder; 7, evaporator; 8, crystallizer; 9, separator; 10, tank for racemization.

temperature by treatment with acetic anhydride in acetic acid. In addition, amino acids are racemized by enzymes (racemases); however, this is not a general method.

2.7. Asymmetric Synthesis

The asymmetric synthesis of L- or D-amino acids is of great value because optical resolution becomes unnecessary. Among the known methods of asymmetric synthesis, enantio-differentiating (selective) catalytic reaction[28] seems to have industrial potential. In 1968, L-dopa was obtained by asymmetric synthesis using *Wilkinson's* complex catalyst carrying an optically active phosphane ligand as shown in Figure 7[29]. This practical method attracted attention because

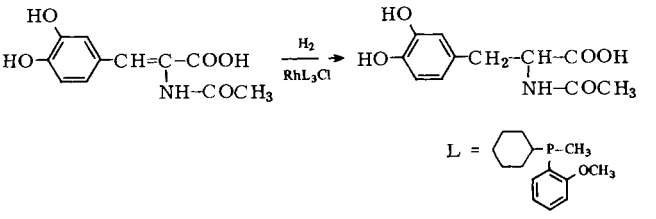


Fig. 7. Asymmetric synthesis of L-dopa.

the product is a relatively expensive amino acid, and the intermediate is fairly stable. Apart from economic aspects, asymmetric synthesis has the inherent restriction that the precursor carbon atom becoming the α-carbon atom of a desired amino acid must be sp^2 hybridized. Therefore, feasibility of asymmetric synthesis as an industrial process seems to be limited to a few special cases.

As described above in Sections 2.2, 2.3, and 2.4, the fermentation method, the enzymatic method, and the synthetic method are all employed for the production of amino acids. Fermentation methods using the latest techniques of microbial genetics afford numerous amino acids. An advantage of the fermentation method is the low cost of raw material; natural L-amino acids can be obtained from inexpensive carbon and nitrogen

sources. However, the fermentation method profits less on scale-up than the synthetic method. Furthermore, much labor and time is necessary for isolation or purification of the product because its concentration is generally low and by-products are often formed.

On the other hand, the synthetic method requires processes of optical resolution and racemization, since DL-amino acids are usually obtained. However, there are some advantages to be expected from large scale operation of the synthetic method, and isolation and purification of the product are easy.

It would be pointless to carry out enantio-differentiating Strecker or Snyder reactions, since both cyanohydrin and hydantoin are readily racemized during hydrolysis to amino acid. However, it would be a practicable method if enantio-differentiating catalytic hydrolysis were to become feasible. The enzymatic method for L-lysine production from DL-amino caprolactam (cf. Fig. 4) can be cited as an example. If the following reaction could be carried out with an enantio-differentiating catalyst, it would hold great promise for economic reasons and also because of its wide applicability:

$$R{-}CHO + R'CONH_2 + CO \xrightarrow[Co_2(CO)_8]{} R{-}\underset{\displaystyle NHCOR'}{\overset{\displaystyle |}{CH}}{-}COOH$$

Therefore, in the face of rising costs of plant construction and labor, synthetic methods appear, in some cases, more economical for the production of amino acids.

The enzymatic method assumes an intermediate position between fermentation and synthesis. Thus, it affords optically active amino acids and isolation is simple owing to high product concentrations. Moreover, the enzymatic method can be carried out continuously and automatically by employing immobilized enzyme or immobilized cell systems. Application of the enzymatic method to appropriate intermediates obtained by chemical synthesis also seems to be promising.

3. Utilization of Amino Acids

Amino acids are the main components of protein which is one of the three essential nutritional components.

All the amino acids occurring in proteins are in the L form, and only amino acids of this form are utilized in the living body. Thus, L-amino acids are usually[*] required for human and animal consumption.

3.1. Fortification

The nutritive value of protein depends on the quantity and balance of its constituent essential amino acids. Table 4 shows the estimated daily requirements of adults. We must take these essential amino acids daily and simultaneously; even if only one essential amino acid is supplied at an inadequate rate or at a different time from other amino acids, then the level of utilization of all the amino acids is lowered to that of the deficient amino acid ("limiting amino acid"). The amino acid content of most cereals is not well balanced. The nutritional value of protein can be improved by modification of amino acid balance; this is done by addition of small amounts of limiting amino acid(s) to food and feed. This amino acid fortification is significant not only nutritionally but also economically.

Table 4. Estimated daily amino acid requirements of adults[30].

Amino acid	Amount [mg/kg]
Isoleucine	10
Leucine	14
Lysine	12
Methionine + cystine	13
Phenylalanine + tyrosine	14
Threonine	7
Tryptophan	3.5
Valine	10

Amino acid fortification of animal feeds is practiced on a large scale. In particular, methionine and lysine are now indispensable for the production of animal feeds. In compound feeds, fishmeal or soybean meal generally serves as protein source. Although the amino acid composition of fishmeal is nutritionally good, prices and supplies fluctuate. The supply of soybean meal is more stable and its use in compound feeds is increasing. Methionine is the first limiting amino acid in soybean protein, and admixture of methionine very effectively improves its nutritional value. Methionine supplementation could also be applied to single cell protein (SCP) which is also low in methionine.

Almost all DL-methionine now produced is used for fortification of feeds and the demand for methionine is consequently increasing year by year. The annual world production of compound feeds supplemented with methionine is estimated as 200 million tons.

Corn is also an important vegetable protein source for animal feed, but like other cereal grains it is deficient in lysine. When the proportion of corn is high and that of soybean meal is small in a mixed feed, lysine supplementation is needed to increase nutritional efficiency. With the recent rise in price of soybean, lysine fortification has been increasing. The annual world demand for lysine is estimated to exceed 20 thousand tons.

Most cereals except corn, are deficient in threonine. In corn, tryptophan is also a limiting amino acid besides lysine. Hence tryptophan may be used for nutritional improvement in areas where corn is the staple diet.

The increase in world population and poor crops have had a serious impact on nutrition, especially on protein supplies. Better utilization of plant foods seems to be the most promising approach to the solution of this problem. Many studies have demonstrated that lysine fortification of foods such as bread and rice effectively raises the nutritional quality of cereal protein. However, lysine fortification has not been extensively applied to cereal products. Admixture of methionine and lysine to compound feed saves plant protein resources used for the production of animal protein. Food and feed compete with each other for the same limited resources.

With regard to world food supplies, we believe that a food crisis can be avoided if consumption of cereals and grains as foods and feeds is controlled on a world wide scale and efficient use is made of amino acids.

[*] Methionine is an exception (see Section 2.4).

3.2. Use of Amino Acids for Food Processing

The taste of foods is as important a factor as their nutritional value. Considering that amino acids provide one of the main contributions to food taste, the significance of amino acids in food processing is easily understood. The essential taste of foodstuffs is frequently due to free amino acids. In particular, L-glutamic acid, which is ubiquitous in animal and vegetable foods, can enhance or improve the taste and flavor of natural foodstuffs. This amino acid also synergistically intensifies the taste of nucleotides such as sodium inosinate, which are mainly responsible for the taste of animal foods[31]. Thus, sodium L-glutamate (MSG) is an indispensable additive for dehydrated soup and many other processed foods. It has been widely marketed, alone or combined with a nucleotide, for cooking or table-seasoning in Asian countries, the United States, and Latin America.

Besides glutamic acid, several other amino acids, such as L-aspartic acid, L-alanine, and glycine, are also employed to a lesser extent in food processing. L-Alanine and glycine, which exhibit a refreshing sweet taste, occur at high levels in shrimps and clams. So they are recognized to be essential taste components of fishery products.

Bitterness is one of the factors comprising a complex food taste. Many L-amino acids and peptides have a bitter taste. In cheese, for example, cyclo(L-tryptophanyl-L-leucyl) was found to be one of the bitter components[32]. Cyclo(L-valyl-L-phenylalanyl) is responsible for the bitterness of cocoa beans[33].

Since the accidental discovery of the pronounced sucrose-like taste of L-aspartyl-L-phenylalanine methyl ester (APM) in 1968, numerous reports and patents have appeared on sweet peptides. The practical use of APM, which is 150 times as sweet as sucrose, is now under development.

In food processing, the browning reaction gives rise to some special flavors or aromas. Heating of mixtures of finely divided carbohydrate, pentose, and sulfur-containing amino acids yields expanded porous products with meat-like flavor[34]. A chocolate-like flavor is formed by heating a branched-chain amino acid with sugars[35]. The browning reaction products from amino acid and sugar also exhibit a marked antioxidant effect[36].

In addition, amino acids have many other uses in food processing; meat preservation[37]; beer preservation[38], inhibition of denaturation of frozen meat[39], and improvement of the quality of sake[40].

3.3. Medical Uses

3.3.1. Nutritional Preparation

Since the introduction of parenteral infusion of crystalline amino acids in Japan in 1956, the use of pure amino acids in place of protein hydrolyzates has been increasing because the infusions based on crystalline amino acids show higher nutritional value and fewer adverse effects than those employing protein hydrolyzates. It is estimated that the annual world demand for these infusion preparations is 10 million vials containing 500 ml of a 5 to 10% amino acid solution. Most of the modern amino acid infusions contain approximately fifteen amino acids including the essential ones. The infusion is usually injected into a peripheral vein.

In 1968, *Dudrick et al.* reported a new technique in which relatively high concentrations of amino acids are injected *via* a central vein together with glucose, minerals, and vitamins[41]. This hyperalimentation technique permits adequate parenteral nutrition and has extended the use of amino acid infusions.

"Chemically defined diets" (CDD) have been developed for oral administration to patients with disorders of the digestive tract. Amino acids are used as the nitrogen source in these diets, in which all the necessary nutrients are supplied in chemically defined form.

3.3.2. Therapeutic Agents

Some amino acids playing specific physiological roles are used for therapeutic purposes. L-Arginine is related to biosynthesis of urea, and used for the treatment of hepatic disorders. Arginine administration is also said to be effective against male infertility resulting from arginine deficiency[42].

L-Tryptophan has been reported to be effective as a sleep inducer[43] and has been used as an antidepressant[44]. Oral administration of L-5-hydroxytryptophan improves the muscle tone of infants with Down's syndrome[45].

Gerber[46] has reported that large oral doses of L-histidine may relieve the symptoms of rheumatoid arthritis. L-Dopa is employed practically in the treatment of Parkinson's disease.

Amino acids are also utilized as raw materials for the synthesis of peptides used as medicines and diagnostics such as glutathion, thyrotropin releasing hormone (TRH), pentagastrin peptide, luteinizing hormone releasing hormone (LHRH), and so on.

3.4. Miscellaneous Uses

Various industrial uses of amino acids have been developed utilizing their physicochemical characteristics. Since industrial materials have to be low in price, inexpensive amino acids are used when suitable. Sodium acylglutamate is employed as a weakly acidic soap which has approximately the same pH as human skin. Poly-γ-glutamate is utilized as a coating material for artificial leather, to which it imparts a natural feel.

In addition, amino acids are employed in cosmetics as buffering or moisturizing agents.

4. Conclusion

The amino acid industry has grown to its present size as a result of technical innovations in manufacturing methods and in applications. However, it seems that this growth has now reached a plateau. This means that the first stage in the epoch-making developments of technology and marketing has now come to a close.

Manufacturing processes for amino acids have advanced rapidly in recent years. It can be said that the technology has reached a level at which almost all amino acids can be supplied to meet any demand, price remaining the only limit. The large market for amino acids, *e.g.* use of methionine, lysine, and monosodium glutamate as additives for foods

or animal feeds, is closely related to problems of world population and natural resources, together with changes in politics, social system, thought, and taste. It therefore seems difficult to predict future amino acid demands. Moreover, there are also economic restrictions; the lower the price the greater the demand, and the higher the price the smaller the demand. In spite of these problems, a favorable long term future can be predicted for the amino acid industry.

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The Versatility of Tertiary Phosphane Ligands in Coordination and Organometallic Chemistry

By Ronald Mason and Devon W. Meek[*]

Tertiary phosphanes form kinetically stable complexes with formal oxidation states of the metal ranging from +IV to −I ("electronic versatility"). Variously substituted phosphanes and polydentate, chelate forming phosphanes and polyphosphanes can be synthesized ("steric versatility"). Studies on complexes containing such ligands provide, *inter alia*, useful information about the metal-phosphorus bond, about the steric effects of the phosphane ligand, and about reactions of coordinated phosphanes.

1. Introduction

A large number of alkyl- and aryl-phosphanes are now available following the pioneering syntheses of tertiary phosphanes and arsanes by *F. G. Mann*[1a] and *J. Chatt*[1b]. *Chatt*'s pioneering studies on organometallic and metal-hydride chemistry made extensive use of tertiary phosphane ligands to stabilize M—H, M—C, M—olefin, and M—acetylene bonds[1c]. A comprehensive discussion of the very large number of transition metal-phosphane complexes would require a large book; such extensive reviews are available[2]. Our objective in this article is to present a critical discussion of four currently important topics in the chemistry of transition metal complexes. Thus we present a reasonably objective survey of the minimum experimental observations needed to support our views on the nature of the metal-phosphorus

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bond, the role of steric effects in phosphane complexes, special effects of polyphosphanes, and reactions of coordinated phosphanes.

The number and variety of tertiary phosphane complexes of transition metal ions that have been synthesized and characterized have accelerated rapidly during the past twenty years. Compared with neutral N- and O-donor ligands, the electronic versatility of tertiary phosphane ligands appears to be reflected in kinetically stable complexes with formal oxidation states of the metal ranging from +IV to −I[2]; this feature is often attributed to the metal-phosphorus bond having both σ- and π-components, the relative importance of which may be qualitatively anticipated from the Electroneutrality Principle.

The steric versatility of tertiary phosphanes derives from the purposeful variation of the substituent groups on phosphorus and from the synthesis of polydentate phosphanes, both of which can provide for a definition of particular stereochemistries and electronic configurations of complexes so that, *inter alia*, coordinatively unsaturated, reactive species of interest in homogeneous catalytic reactions can be isolated. More generally, these studies have ensured that the influence of steric effects on the thermodynamic and kinetic properties of transition metal complexes are being properly recognized and partially quantified after twenty years of almost total preoccupation with crystal and ligand field theories of electronic effects.

2. The Metal-Phosphorus Bond

A metal-phosphorus bond, like a transition metal-olefin bond, has from simple symmetry considerations alone, both σ- and π-components. We recognize now that metal to ligand π-bonding in olefin complexes is best discerned by considering the overall stereochemistry of the coordinated ligand, and not simply by the length of the coordinated bond[3]. The arguments for dπ-dπ bonding in metal-phosphane complexes are, for the most part, however, derived from equilibrium bond lengths since a metal-phosphorus bond distance is often suggested as being shorter than the sum of covalent radii and to be dependent on the nature of substituent groups. Some representatives of different coordination geometries are given in Table 1 to illustrate the effects of coordination symmetry (d^{10} systems) and different phosphane substituents (d^8 systems) on the M—P bond distances.

The internuclear distance in a metal-phosphorus bond should reflect the electronic configuration, oxidation state and coordination number of the metal; steric and electronic properties of the substituent groups on the tertiary phosphane; and the nature of the other ligands making up the coordination sphere. The only systematic study of the dependence of metal-phosphorus bond lengths on electronic configuration showed that in the complexes $[MCl_4L_2]$ and $[MCl_3L_3]$ (M = W, Re, Os, Ir, Pt; L = PMe_2Ph)[12a], the M—P bond lengths change by 0.05 Å per unit change of electron configuration while the corresponding M—Cl bond lengths change by only 0.01 Å (Fig. 1)[12b]; it was clear also that the break at the d^5 configura-

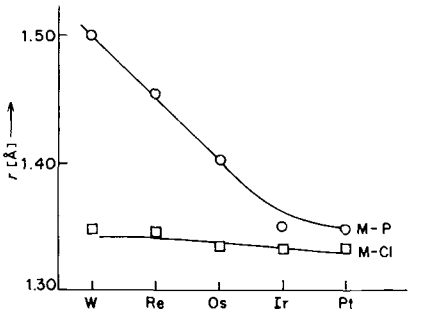


Fig. 1. Calculated metal covalent radii (—) in complexes of type $[MCl_4L_2]$ and $[MCl_3L_3]$ (L = PMe_2Ph); circles are the observed metal-phosphorus bond distances minus the covalent radius of phosphorus, 1.05 Å; squares are the observed metal-chlorine bond distances minus 0.99 Å, the covalent radius of chlorine.

tion is due to the population of metal-ligand antibonding levels. The experimental data received a quantitative explanation through a simple maximum overlap model[13], the essence of which was to establish that maximum overlap provides for the tertiary phosphane ligands pre-empting much metal 's' electron character in their σ-bonds. The radial dependence of the metal 6s electron wave function varies rapidly with electronic configuration; thus, metal covalent radii, calculated from both metal-phosphorus and metal-chlorine distances, reflect the observed results to better than 0.01 Å.

It is not surprising that bond lengths in complexes of metals in their +IV oxidation state show no evidence for metal

Table 1. Some metal-phosphorus bond lengths in d^8 and d^{10} metal complexes.

Electronic configuration	Complex	Approximate symmetry of ligand field	Bond length M—P [Å]		Ref.
d^8	$[RhH(PF_3)(PPh_3)_3]$	Trigonal bipyramidal	Rh—P(PF_3) Rh—P(PPh_3)	2.16(1) 2.34(1)	[4]
	$[RhH(PPh_3)_4]$	Pseudotetraedral		2.34(1) 2.34 or 2.39	[5]
	cis-$[PtCl_2\{Ph_2PCH_2CH_2P(CF_3)_2\}]$	Planar	Pt—P($P(CF_3)_2$) Pt—P(PPh_2)	2.168(3) 2.244(2)	[6]
d^{10}	$[Pt(Pcy_3)_2]$ [a]	Linear		2.231(4)	[7]
	$[Pt(PPh_3)_3]$	Trigonal		2.23—2.25(1)	[8]
	$[Pt(alkene)(phosphane)_2]$ $[Pt(alkyne)(phosphane)_2]$	Planar		2.28 (average)	[9]
	$[Pt(PF_3)_4]$	Tetraedral		2.230(10)	[10]
	$[Pt\{CH_3C(CH_2PPh_2)_3\}_2]$ [b]	Slightly distorted tetraedral		2.286(8) (average)	[11]

[a] cy = Cyclohexyl. [b] $[Pt(triphos)_2]$; cf. *(12)*.

to ligand π-bonding. Bond distances, however, have been cited as evidence of π-bonding effects in planar complexes of palladium(II) and platinum(II). *Mather et al.*[14], showed that there was a good correlation between Pt—P bond lengths and $^1J_{Pt\text{-}P}$ coupling constants and they also summarized plausible evidence that the coupling constants are dominated by the Fermi contact term and by the s-electron bond order in the platinum-phosphorus molecular orbital. Their data[14, 15] are shown in Figure 2 together with some representative data for platinum(0) complexes which, *prima facie*, should demonstrate condiserably more metal to ligand π-bonding.

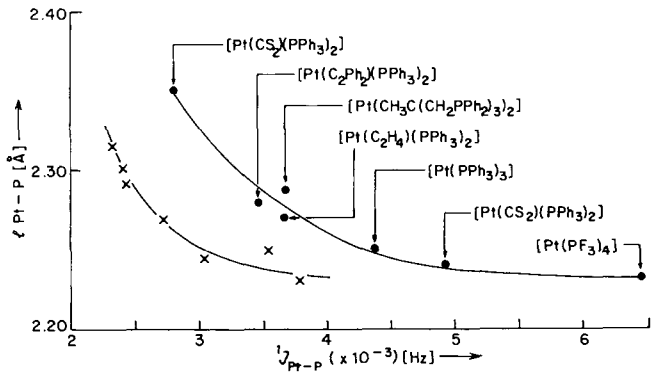


Fig. 2. Platinum-phosphorus bond lengths l (Pt—P) as a function of the coupling constants $^1J_{Pt\text{-}P}$. The curve with ×'s is *Pidcock*'s original correlation based on platinum(II) complexes [14]; the curve with •'s is our plot of data on formally platinum(0) complexes.

A bond length can be related to the σ- and π-bond orders,

$$l_{M-P} = \sigma_{(M)} + \sigma_{(P)} - k\pi_{M-P} \qquad (a)$$

where σ_M and σ_P are σ-covalent radii of the metal and phosphorus atoms, k is a constant and π_{M-P} is the metal-phosphorus π-bond order. *Coulson*[16] first showed for carbon-carbon bonds that σ(M) and σ(P) are a function of formal hybridization states, and he defined the σ-covalent radius as the distance from the nucleus to the centroid of electron density,

$$\sigma = \frac{\int r(\Psi(\lambda))^2 \, d\tau}{\int (\Psi(\lambda))^2 \, d\tau} \qquad (b)$$

where

$$\Psi(\lambda) = s + \lambda p.$$

Covalent σ-radii of phosphorus, using Clementi-Raimondi wave functions[17], can be calculated quite simply in this way. The formal hybridization states of the coordinated phosphorus lone pair orbitals in PF_3 and PPh_3 complexes can be estimated[16] from the respective F—P—F and C—P—C bond angles of 98 and 105°; obviously the PF_3 lone pair has more 's' electron character and the calculated centroid is 0.03 Å shorter than that for the PPh_3 ligand. This difference is almost sufficient to explain the metal-phosphorus bond length difference between $[Pt(PF_3)_4]$ and $[Pt\{CH_3C(CH_2PPh_2)_3\}_2]$, where we can assume initially that the metal σ-covalent radii are identical; therefore, at most only 0.03 Å should be attributed to $M_{d\pi} \rightarrow P_{d\pi}$ multiple bonding.

In the adducts $B_2H_4 \cdot 2PF_3$[18] and $B_2H_4 \cdot 2PPh_3$[19] the B—P bond lengths are 1.85(3) and 1.93(1) Å respectively; in these boron complexes π-bonding cannot be significant. The difference in the two B—P bond distances is comparable to that of the Pt—P bonds and again should be explained by σ-electronic effects. For $[Pt(PR_3)_2]$, $[Pt(PR_3)_3]$ and $[Pt(PR_3)_4]$ the Pt—P bond lengths show an essentially uniform increase of ≈0.02 Å as the metal changes its formal σ-hybridization state from sp to sp^2 to sp^3. Equation (b) for the covalent radii, coupled with the Basch-Gray wavefunctions[20], predicts exactly this difference in spite of the number of potential π-bonding orbitals varying from one complex to the next. The much larger difference in the rhodium(I)–phosphorus bonds[4, 5] is more difficult to analyze unequivocally, because of the very different σ-electron framework in $[RhH(PF_3)(PPh_3)_3]$ and $[RhH(PPh_3)_4]$.

Apart from fluoro-substitution at the phosphorus atom, the M—$P(R^1R^2R^3)$ bond length is not very sensitive to the substituent groups, R^1, R^2 and R^3, provided they are not very sterically demanding. Thus in *cis*-$[PtCl_2(PMe_3)_2]$ and *cis*-$[PtCl_2(PMe_2Ph)_2 \cdot HgCl_2]$ the Pt—P bond lengths are 2.248(9) and 2.255(5) Å, respectively[21, 22]; in *cis*-$[PtCl_2(CO)(PMe_2Ph)]$ and *cis*-$[PtCl_2(CO)(PPh_3)]$ they are 2.264(2) and 2.282(2) Å[23, 24]. However, such substituent changes have marked effects on reactivities.

The effect, on metal-phosphorus bond lengths, of varying the electronic properties of the ligands *cis*- and *trans*- to the bonds is, again, well documented for planar complexes of platinum(II). The Pt^{II}—Cl bond length has been widely used as a yardstick for measuring the relative *trans*-influences of coordinated ligands[25, 26]; the tertiary phosphane ligand is comparable, in its *trans*-influence, with hydride and σ-bonded carbon ligands, there being a simple correlation, in the absence of metal to ligand π-bonding, between a ligand's electronegativity and its *trans*-influencing properties[25]. Equally one can recognize, from a systematic survey of bond lengths in Pt(II) complexes[27], that the platinum-phosphorus bond is determined roughly by the σ-donor properties of the *trans*-ligand, the mean value ranging from 2.22 Å (*trans* to Cl), 2.29 Å (*trans* to C), 2.30 Å (*trans* to P), to 2.33 Å (*trans* to Ge). Not surprisingly, the range is only one-half that of the Pt^{II}—Cl bond length for the same variety of *trans*-ligands. This result can be anticipated from simple electronegativity considerations and from a molecular orbital view of the X—Pt—Y fragment, which imagines that the *trans*-influence on a particular ligand is greatest when it has maximum overlap with metal pσ-electrons.

The effect, on metal-phosphorus bond lengths, of changing ligands *cis* to the M—P bond is more difficult to delineate; it is certainly smaller in magnitude than that associated with their *trans*-influence. A clear cut demonstration of the *cis*-influence is available from the bond lengths in $[RhCl(PPh_3)_3]$[28, 29] and $[RhCl(C_2F_4)(PPh_3)_2]$[28]: the Rh—Cl bond lengths are identical, within experimental error, at 2.382(5) and 2.375(8) Å, while the Rh—P bond lengths (*trans* to P) average 2.328(4) and 2.372(8) Å, respectively. A similar picture is clear from the survey of *Manojlović-Muir* and *Muir*[27]: Pt^{II}—P bond lengths *cis* to σ- and π-donors (*e.g.* Cl^-) average 2.215(4) Å in complexes such as *cis*-$[PtCl_2(PR_3)L]$; if L be a weak Lewis acid (carbene, isocyanide) the bond length increases to 2.242(2) Å while for moderate

π-acceptors (L = CO), the bond length averages 2.272(8) Å; the Pt^{II}—Cl bond lengths vary by up to 0.04 Å in the opposite sense so that steric effects, according to *Muir* and *Muir*[27], can be discounted.

The question of interest is whether the *cis*-influence must be taken as reflecting π-acid behavior of the tertiary phosphanes, such as was suggested earlier[28]. There is now magnetic resonance evidence[30, 31] that the σ-bond formed between alkenes, alkynes and platinum(II) has a significant s-electron component and competition with a similarly demanding tertiary phosphane, but not with the chloride ligand, may be sufficient to rationalize the observed trends. Little of quantitative value, however, can be expressed at present.

In summary, we take the view that the electronic versatility of the phosphane ligand is largely a σ-electron effect, there being little evidence for π-bonding effects in the metal-ligand bond lengths. The Electroneutrality Principle will be satisfied when low valent metal ions use the relatively contracted 's' orbital on the phosphorus atom, high valent metal ions having more charge transfer through the σ-framework *via* the use of the more radially extended phosphorus 3p orbitals. Such a suggestion is consistent with the correlation between bond lengths and coupling constants shown in Figure 2 in that, for a given bond length, the $^1J_{Pt\text{-}P}$ value is greater for platinum(0) complexes than for platinum(II) complexes. The variation in s-p character is substantial when ligands with different substituent groups are coordinated to a given metal; for example, ESR studies on [CoL(TPP)] (TPP = tetraphenylporphyrin) show[32] that the percent s character changes from 68% when L is PF_3, to 51% (L = $P(OMe)_3$), to 36%, 28, and 27% when L = PMe_3, PMe_2Ph, and PEt_3, respectively; this would be an admirable extended series for crystallographic studies and correlation of metal-ligand bond lengths with independently determined electron distribution parameters.

3. Steric Effects of Tertiary Phosphane Ligands in Transition Metal Complexes

The distinction between electronic and steric effects of ligands is often no more than a semantic one. In the present context, an increase in substituent bulkiness will serve to increase the angle between substituent groups and will, in a formal way, localize more 'p' character in the phosphorus lone pair. An increase in the metal-phosphorus bond length will follow, which could have had its origins more directly from secondary (non-bonded) rather than primary valence interactions. Only rarely have these complementary effects been separated.

An obvious starting point in our discussion is the group of phosphane complexes of d^{10} ions (Ni^0, Pd^0 and Pt^0). *Musco et al.*[33] showed that the coordination number of the zerovalent palladium complexes may be 2, 3 or 4, the relative preference in forming coordinatively unsaturated species being $PMe_3 \approx PMe_2Ph \approx PMePh_2 < PPh_3 \approx PEt_3 \approx P(n\text{-}Bu)_3 < P(benzyl)_3 < P(i\text{-}Pr)_3 < P(cyclohexyl)_3 \approx P(t\text{-}Bu)_2Ph$; the sequence is obviously not well related to changing basicity but rather to the steric demands of the tertiary phosphanes. A very similar picture emerged from *Tolman*'s studies[34] of nickel(0) species: for the equilibria

$$[NiL_4] \overset{K_d}{\rightleftharpoons} [NiL_3] + L$$

K_d ranges from $< 10^{-9}$ for PMe_3 at 70°C, 1.2×10^{-2} for PEt_3, 5×10^{-2} for $PMePh_2$ to > 10 for PPh_3. These important studies were complementary to an earlier attempt to define the steric requirements of a ligand in terms of its 'cone angle', the apex angle of a cylindrically symmetric cone centered at 2.3 Å from the phosphorus atom and enveloping, in a van der Waals contact sense, the outermost atoms of the ligand. Cone angles, measured relatively crudely from molecular models, vary from 118° (PMe_3) to values of 132°, 136° and 145° for PEt_3, $PMePh_2$ and PPh_3, respectively[35]. We shall return later to the cone angle concept; but, together with studies of the dissociation of copper(I)[36] and cobalt(I)[37] species, there seems little doubt left that ligand bulkiness, however it may be measured, is a dominant factor in determining the metal coordination number in solution and the bonding potential and reactivity of the coordinatively unsaturated species. A striking example of the latter has been the demonstration, by *Otsuka et al.*[38], that while $[Pd\{P(t\text{-}Bu)_2Ph\}_2]$ readily forms the dioxygen adduct $[PdL_2O_2]$, the somewhat more crowded fourteen electron species $[Pd\{P(t\text{-}Bu)_3\}_2]$ is stable.

Two other remarks should be made. The platinum-phosphorus bond lengths in $Pt(Pcy_3)_2$[6] and *trans*-$[PtH_2(Pcy_3)_2]$[39] (cy = cyclohexyl) are not significantly different at 2.231(4) and 2.25(1) Å respectively; since the *trans*-influence of the hydride and phosphane ligands are generally very similar, one can deduce that steric effects in the dihydrido complex are negligible. In *trans*-$[PtI_2(Pcy_3)_2]$[40], however, the Pt—P bond length increases to 2.371(2) Å compared with 2.315(4) Å in *trans*-$[PtBr_2(PEt_3)_2]$[41] and this may be fair evidence that *cis*-interactions can cause bond lengthening of the order of 0.05 Å or so. We need to enter the caveat that, electronically as well as sterically, the two halide ions make somewhat different demands on the metal. A much more important comment, however, relates to the observations that in many low-valent, electron deficient species there are non-primary valence interactions of carbon-hydrogen bonds with the metal[29]. Thus, two ortho-hydrogen atoms are positioned at *ca.* 2.7 Å from the metal in $[Pd\{P(t\text{-}Bu)_2Ph\}_2]$[42] and, with the phosphorus atoms, provide for a planar coordination geometry of the metal which persists in solution. These metal-hydrogen interactions appear to be necessary, if not sufficient, for facile intramolecular oxidative-addition reactions[43] and are further examined below.

Steric demands of coordinated phosphanes may be insufficient to provide for low coordination numbers but adequate to impose distortions from an anticipated coordination geometry. Tris(triphenylphosphane)rhodium(I) chloride is an important complex, from the standpoint of its catalytic properties[44] and its structural dimorphism[29]; the latter allows ligand conformations and coordination geometries to be examined in detail. Red crystals (α isomer) are obtained when a solution of triphenylphosphane in ethanol is added to an ethanolic solution of rhodium trichloride; an orange crystalline form (β isomer) is formed when the order of addition is reversed and the solution of rhodium trichloride is added very slowly to a concentrated solution of triphenylphosphane in ethanol. Molecular stereochemistries[29] are shown in Figure 3 and represent the atomic arrangements projected upon the mean

coordination planes. While the metal-ligand bond lengths in the two isomers are very similar (estimated standard deviations in the metal-ligand bond lengths average 0.005 Å), the distortions from planar coordination symmetry about the metal vary considerably between the isomers. The '*trans*' Cl—Rh—P bond angles are 156.2(2)° (α isomer) and 166.7(2)° (β isomer) while the '*trans*' P—Rh—P bond angles are 152.8(1)° and 159.1(2)°; the r.m.s. deviations, towards tetrahedrality, of the coordinated atoms from the mean coordination plane are 0.43 Å (α isomer) and 0.28 Å (β isomer). By contrast, the structural analysis of [RhCl(ttp)][45] shows it to be more planar, the r.m.s. deviation from the mean plane being only 0.08 Å with the metal-phosphorus bond lengths in the chelating triphosphane being systematically 0.02 Å shorter than those in $[RhCl(PPh_3)_3]$.

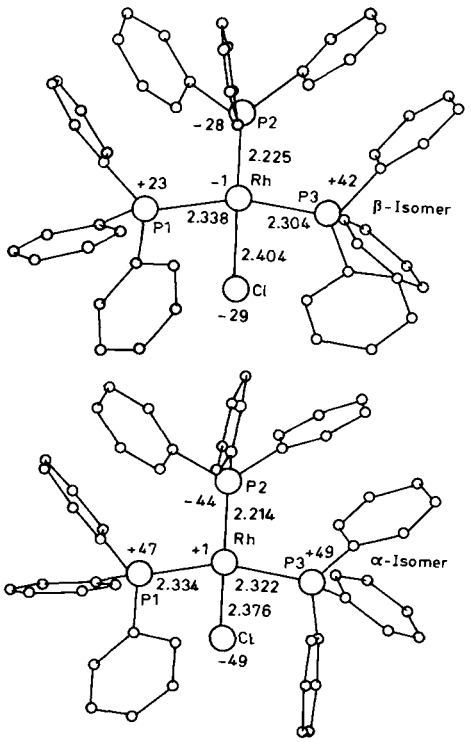


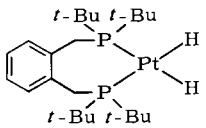
Fig. 3. Atomic arrangements, metal-ligand bond lengths [Å], and deviations from mean coordination planes [$\times 10^2$ Å] in the two isomers of $RhCl(PPh_3)_3$. Above: β-isomer, orange-colored crystals, metastable; below: α-isomer, red crystals, stable.

The orange (β) isomer is metastable with respect to the α form, being converted rapidly on refluxing. The stable isomer has the phenyl rings in a more close packed arrangement with a number of non-bonded H...H, C...H and C...C distances averaging 2.2 Å, 2.6 Å and 2.9 Å respectively; short intramolecular nonbonded C...H contacts between phenyl rings are absent in the metastable β-isomer, a significant result in relation to their importance in stabilizing the conformation of many organic molecules[46]. The solid surfaces enveloping the triphenylphosphane ligands deviate from conical symmetry, the anisotropy in the cone angles often amounting to some 10°. A variety of conformations, separated by small energy differences only, is open to substituent groups, provided there are concerted, cooperative motions of the groups.

The ground state geometries of α- and β-$[RhCl(PPh_3)_3]$ do not provide an obvious explanation for its facile dissociation[44,47], in solution, to $[RgCl(PPh_3)_2]$. The relative weakness of the chemically equivalent rhodium-phosphane bonds and the bond angles in the stable α-isomer of $[RhCl(PPh_3)_3]$ allow the plausible speculation that $[RhCl(PPh_3)_2]$ would be trigonal planar; another possibility would involve two *ortho*-hydrogen atoms occupying axial positions to form a trigonal-bipyramidal structure. A quasi-eighteen electron structure for the rhodium ion (see Section 5) would then follow, but there is no direct evidence for this suggestion[29], nor for an alternative one involving two-electron donation from a phenyl ring[47].

There are many examples of phosphane ligand steric effects on planar-tetrahedral isomerization of complexes[35,48]. Perhaps more interestingly, *cis-trans* isomerism in planar complexes of palladium(II) and platinum(II) was shown[49] to depend on the bulkiness of tertiary phosphane, arsane and stibane ligands. The effect has been elegantly exploited by *Shaw et al.* through the synthesis of macrocyclic tertiary biphosphane complexes[50]; long chain α,ω-biphosphanes of the type $(t\text{-Bu})_2P(CH_2)_nP(t\text{-Bu})_2$ ($n=9$, 10 or 12) form mono-, di- and tri-nuclear macrocyclic complexes with platinum metals in a way which has been interpreted in terms of favorable internal entropy and conformational effects. The structures[51] of these complexes illustrate the strain-free state of the macrocycles; the central methylene fragments have conformations which are identical to those in linear alkanes and long-chain fatty acids.

An interesting variation on the theme of determination of stereochemistry has provided the first *cis*-dihydride of platinum(II), *(1)*[52]. The seven-membered chelate rings allow



(1)

the *tert*-butyl groups to be sufficiently separated but its rigidity prevents the diphosphane from acting as a bridging ligand between two metal atoms.

Apart from determining coordination numbers and symmetries, certain tertiary phosphanes or their derivatives have been used to stabilize unusual oxidation states of metals. The synthesis and structures of two planar iridium(II) complexes, *trans*-$[Ir\{(t\text{-Bu})_2PC_6H_4O\}_2]$ and *trans*-$[Ir\{(t\text{-Bu})_2C_6H_3(OMe)O\}_2]$ have been described[53]. Paramagnetic rhodium(II) complexes $[RhCl_2L_2]$ [L = Pcy_3, P(O-tolyl)$_3$] are available[54] but the reaction of rhodium trichloride with less bulky phosphanes provides the more conventional $RhCl_3L_3$ complexes[55].

4. Metal Complexes of Polyphosphane Ligands

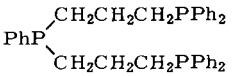
As noted above, tertiary phosphane ligands appear to accommodate a wide range of properties in transition metal complexes, especially since the steric and electronic properties of the ligands can be varied relatively easily by changing the substituents on phosphorus. These advantages of a phosphane ligand can be emphasized by a properly designed chelating polyphosphane. During the past twelve years significant advances have been accomplished in the synthesis of polyden-

tate ligands. Whereas combinations of nitrogen, oxygen, and sulfur donors have utilized the "template effect"[56], polyphosphane ligands have, as yet, been prepared by more conventional organic methods involving Grignard reagents, alkali metal phosphides[57], or addition of a P—H bond to the double bond of a vinylphosphane[58, 59, 60]. In particular, a large number of "tripod-like" potentially tetradentate ligands of the type

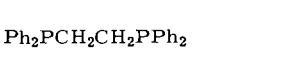


have been investigated by the research groups of *Meek*[61], *Sacconi*[62], and *Venanzi*[63] (usually the connecting chains are *o*-phenylene, ethylene, or trimethylene and one or more of the donor atoms A, B, C, and D is phosphorus).

Many studies have shown that the structure, stability, and magnetic properties of the transition metal complexes of such chelating ligands are sensitive functions of both electronic and steric effects[64]. Compared to a monodentate phosphane, a polyphosphane ligand can provide simultaneously (i) more control on the coordination number, stoichiometry, and stereochemistry of the resulting complex, (ii) an increased basicity (or nucleophilicity) at the metal, and (iii) detailed structural and bonding information in the form of metal-phosphorus and phosphorus-phosphorus coupling constants. For example,



(2), ttp



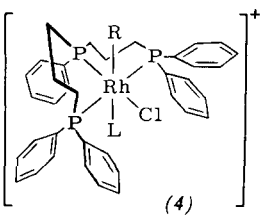
(3), diphos

the trimethylene connecting linkages of triphosphane *(2)* (ttp) provide an ideal "chelate bite" for the larger transition metal ions. The P—Rh—P angles involving chelated rings are $90\pm1°$ in the three complexes $[RhCl(ttp)]$[45], $[RhCl(NO)(ttp)]^+$[45], and $[RhCl(N_2Ph)(ttp)]^+$[65], in contrast to "pinched" P—M—P angles of $82\pm1°$ for Rh^I, Ir^I, and Pt^{II} complexes of ligand *(3)* (diphos)[66, 67]. The 90° P—Rh—P bond angles permit maximum overlap of the phosphorus and rhodium orbitals, which undoubtedly contributes to the planar structure (see Section 3), dissociative stability, and basicity of $[RhCl(ttp)]$ as compared to the stoichiometrically analogous complex $[RhCl(PPh_3)_3]$[68]. The five-coordinate cations $[RhCl(NO)(ttp)]^+$ and $[RhCl(N_2Ph)(ttp)]^+$ are square-pyramidal; the most diagnostic and important structural features of the latter two complexes being that the $[RhCl(ttp)]$ fragment is arranged in the basal plane in both complexes; is similar to that in the parent compound; and that the M—N—O and M—N—N bond angles are bent, with Rh—N—O and Rh—N—N being 131(1)° and 125(1)°, respectively[45].

The structures of both these cations indicate that $[RhCl(ttp)]$ has undergone a single-site oxidative addition and converted the NO^+ and N_2Ph^+ groups, respectively, into the NO^- and N_2Ph^- ligands. This interpretation is also supported by the ^{31}P-NMR spectra *(vide infra)*. Comparable reactions are not available with complexes of equivalent monodentate phosphanes.

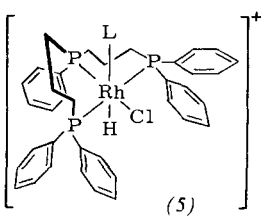
Chemical studies also show that the rhodium atom in $[RhCl(ttp)]$ is quite basic (nucleophilic). The metal center readily functions as a Lewis base toward both neutral acids (*e.g.*, SO_2, BF_3, CO, O_2, X_2, HX, CH_3X, and TCNE) and cationic acids (*e.g.*, CH_3^+, CH_3CO^+, $C_2H_5^+$, and H^+) to give stable, five-coordinate complexes of the type $[RhCl(ttp)\cdot A]$ and $[RhCl(ttp)\cdot A]^+$, respectively[45, 69]. The chelating triphosphane ligand *(2)* (ttp) has increased the apparent basicity of the metal center to the point that $[RhCl(ttp)]$ mimics the reactions of phosphane complexes of iridium(I), *e.g.* $[IrCl(CO)(PPh_3)_2]$ and $[IrCl(PPh_3)_3]$, more closely than it resembles other rhodium-arylphosphane complexes[70].

Although the cationic hydride and methyl complexes $[RhCl(H)(ttp)]^+$ and $[RhCl(CH_3)(ttp)]^+$ are formally analogous, they show striking differences in the tendency to bond a sixth ligand (*e.g.*, CO, CH_3CN, or C_2H_5OH)[69]. The cation $[RhCl(CH_3)(ttp)]^+$ does not form adducts with molecules such as DMSO, SO_2, or C_2H_5OH, whereas the analogous rhodium-hydride cation is stable only as six-coordinate complexes of the type $[RhClHL(ttp)]^+$ *(5)*. Both the methyl and hydride cations add carbon monoxide or acetonitrile and give isolable six-coordinate complexes, but the relative tendency to add CH_3CN or CO is much stronger for the hydride case. The marked difference in chemical properties may be due to different structures of the two complexes [cf. *(4)* and *(5)*].



(4)

R = CH_3, C_2H_5
L = CH_3CN, CO



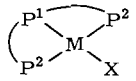
(5)

L = C_2H_5OH, CH_3CN, THF, CO

X-ray results on both the complexes $[RhCl(NO)(ttp)]^+$ and $[RhCl(N_2Ph)(ttp)]^+$ show that a phenyl group on each of the three phosphorus atoms is projected down and forms a small cavity *trans* to the apex ligand[45, 65]. Thus, the most probable metal site for addition of a bulky ligand (*e.g.*, CH_3^+) would be on "top" of $[RhCl(ttp)]$, whereas the small hydride ligand is added after coordination of a solvent molecule and apparently can fit into the cavity, giving a different diastereomer. The basic nature of $[RhCl(ttp)]$ is also demonstrated by protonation and alkylation reactions on a series of *p*-substituted phenyldiazo complexes. IR and ^1H-NMR spectra on $^{15}N{-}{-}^{14}N{-}Ar$ and $^{14}N{-}{-}^{15}N{-}Ar$ isotopically labelled compounds shows that the most basic nitrogen atom is adjacent to rhodium[71, 72], in contrast to the situation in M—N=N—Ph type complexes, where protonation occurs on the nitrogen atom adjacent to the aryl group[73].

The ligand *(2)* (ttp) is well designed for determining the *trans*-influence of ligands *via* ^{31}P-NMR spectra, especially when the metal center has a magnetic nucleus. As a result of the trimethylene connecting chain between phosphorus atoms. P—P coupling through the chain is nearly always <1 Hz[74, 75]. Thus, a planar Rh^I or Pt^{II} complex of type *(6)* gives both $^1J_{M-P^1}$ and $^1J_{M-P^2}$, which reflect simultaneously the *trans*- and *cis*-influence of ligand X. Table 2 shows a marked decrease in Pt—P coupling *trans* to X in the series

$Cl > CH_2CN > H > CH_3$[74], which gives a generally accepted *trans*-influence order. The Pt—P coupling constants for phosphorus atoms *cis* to the same X ligands increase, ableit much



(6)

less rapidly. From our discussion of the correlation between Pt—P bond lengths and Pt—P coupling constants, one could expect to see a significantly longer Pt—P_1 bond distance in the methyl complex compared to the Cl case.

Table 2. ^{31}P coupling constants [74] of $[Pt(ttp)X]^+$ complexes.

X	J [Hz] Pt—P^1 ±2 Hz	Pt—P^2 ±2 Hz	P—P ±1 Hz
Cl	3217	2284	26
I	3230	2319	26
CH_2CN	1911	2445	32
H	1678	2524	29
CH_3	1626	2611	32

A more extensive series of Rh(ttp) complexes has been examined by ^{31}P-NMR[69, 75, 76], and Table 3 presents the data for selected examples. As in the platinum complexes, the relative chemical shifts of P^1 and P^2, as well as the Rh—P^1 and Rh—P^2 coupling contstnts, are sensitive indicators of the bonding properties of the ligand *trans* to P^1 (note that the magnitudes of the Rh—P coupling constants are about one-tenth of the corresponding Pt—P coupling constants, a reflection of the difference in the magnetogyric ratio of the two metals). Figure 4 shows the large change of the chemical shift of P^1 when chloride is replaced by CO, the data on $[Rh(CH_3CN)(ttp)]^+$ showing that the large change is not

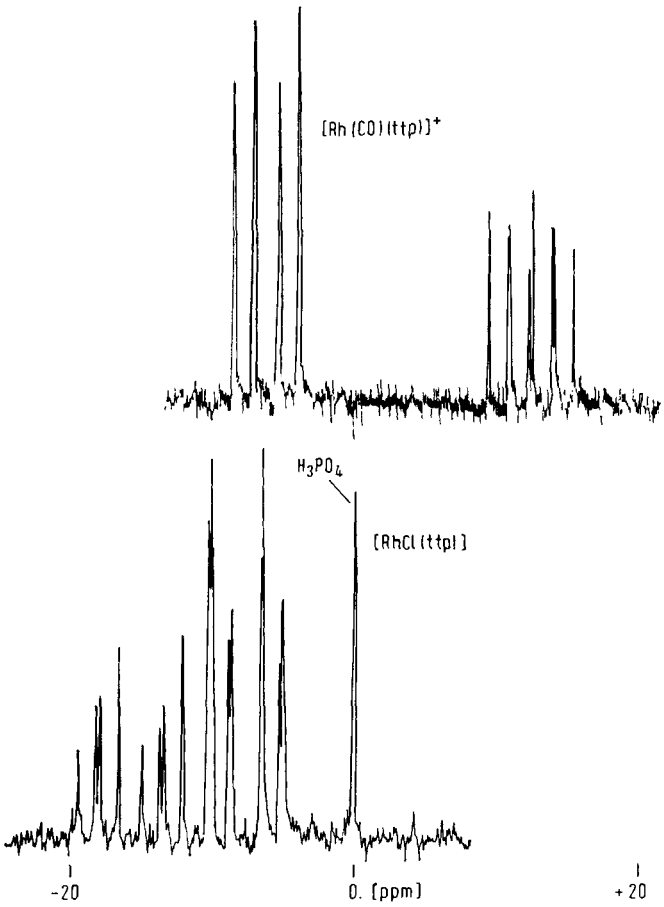


Fig. 4. ^{31}P-NMR spectra (proton-noise-decoupled) of $[Rh(CO)(ttp)]^+$ in acetone (above) and [RhCl(ttp)] in benzene (below) relative to 85% H_3PO_4 as external standard.

Table 3. ^{31}P-NMR data for Rh(ttp) complexes.

Compound	Solvent	δ [ppM] [a] P_1	P_2	P—P	J [Hz] [b] Rh—P^1	Rh—P^2	Ref.
[RhCl(ttp)]	THF, $[D_6]$-acetone	15.8	8.0	52.0	163.0	129.0	[75]
$[Rh(N_3)(ttp)]$	THF, $[D_6]$-benzene	16.78	7.33	53.6	152.2	131.6	[75]
$[Rh(ttp)(CH_3CN)]PF_6$	Acetone, $[D_6]$-acetone	12.45	8.93	52.4	151.5	123.0	[75]
$[Rh(ttp)(CO)]PF_6$	Acetone, $[D_6]$-acetone	−12.01	6.46	52.0	113.3	114.3	[75]
$[RhCl(NO)(ttp)]PF_6$	CH_2Cl_2, $[D_6]$-acetone	10.8	2.1	30	139	106	[76]
$[RhCl(CH_3)(ttp)]FSO_3$	CH_2Cl_2, $[D_6]$-acetone	11.2	1.1	33	115	93	[76]
$[RhHCl(CO)(ttp)]PF_6$	CH_2Cl_2, $[D_6]$-acetone	1.1	4.9	38	90	81	[76]

[a] Value relative to external 85% H_3PO_4, with positive numbers being downfield from the standard.
[b] Resolution for the coupling constants of the first four compounds is 0.4 Hz, for the last three compounds ±1 Hz.

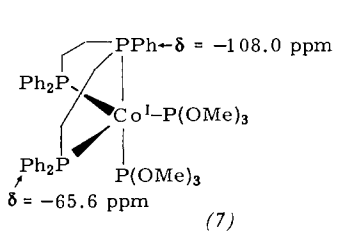
due simply to the formation of a cation. The magnitudes of the Rh—P coupling constants decrease when rhodium(I) is oxidized to rhodium(III)[75, 77]. A correlation between Rh—P bond distances and $^1J_{Rh-P}$ values, similar to the platinum examples discussed in Section 2, will probably develop when more data on rhodium-phosphane complexes become available. In the case of [RhCl(ttp)], the $^1J_{Rh-P}$ values of 163.0 and 129.0 Hz correspond to Rh—P bond distances of 2.201(2) and 2.288(1) Å[65], respectively, while the $^1J_{Rh-P}$ values of 139 and 160 Hz correspond to Rh—P bond distances of 2.282(4) and 2.374(3) Å, respectively, in the five-coordinate nitrosyl cation $[RhCl(NO)(ttp)]^+$[65]. The Rh—P coupling constants for $[Rh(CO)(ttp)]^+$ suggest that the larger *trans* influence of carbon monoxide would be significantly longer than for [RhCl(ttp)] and comparable to the Rh—P^2 distances.

P^{31} coordination chemical shifts ($\Delta = \delta_{complex} - \delta_{free\ ligand}$) depend on the ring size in chelated phosphane ligands. Large downfield shifts are generally observed for 5-membered chelate rings (Table 4). If a phosphorus atom is the bridgehead of two or three 5-membered rings as in *(7)* and *(8)*, respectively,

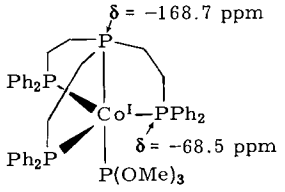
Table 4. ^{31}P-NMR data [78] for complexes of the type $[W(CO)_4\{Ph_2P(CH_2)_nPPh_2\}]$.

	$n=1$	$n=2$	$n=3$
$\delta_{complex}$ [ppm]	+ 23.6	− 40.1	0.0
$\delta_{free\ ligand}$ [ppm]	+ 23.6	+ 12.5	+ 17.3
Δ [ppm]	0.0	− 52.6	− 17.3
$^1J_{W-P}$ [Hz]	202	231	222

the large downfield shift is nearly additive for each additional chelate ring[78,79].



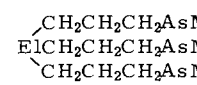
(7)



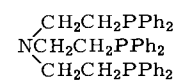
(8)

Poly(tertiary phosphane) ligands can be used to determine magnetic states and coordination stereochemistries by varying the types of donor atom sets, the chelate bite angle, and by introducing sterically demanding substituent groups. For example, wide variations in the nature of the ligand donor set (*e.g.* N_4, N_3P, N_2P_2, NP_3, and P_4) have been achieved by *Sacconi et al.*[62] and *Meek et al.*[61,80,81] through the use of "tripod-like" ligands.

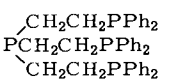
Owing to their extremely flexible nature, tripod ligands such as *(9)*—*(12)*, which contain either ethylene or trimethylene connecting chains, can form complexes with different coordination numbers (six[82,83], five[61,81,84,85] and four[87,88]) and different stereochemistries (octahedral[82,83], trigonal bipyramidal[61,81,84,86], square pyramidal[85],



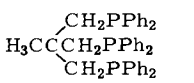
(9), El = P, As, Sb



(10), np_3



(11), pp_3



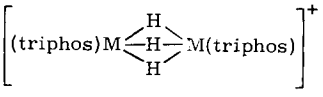
(12), triphos

planar[87], trigonal pyramidal[88], and distorted tetrahedral[89]). Such flexible ligands permit the metal to dictate the preferred coordination number and geometry. The structure of $[CoI(np_3)]I$ is a distorted square pyramid[85], whereas the structure of the analogous nickel(II) complex $[NiI(np_3)]I$ is a trigonal bipyramid[84], with crystallographic C_3 symmetry. These two complexes serve to illustrate a general trend among low-spin, five-coordinate nickel(II) and cobalt(II) complexes of tripod ligands—that the nickel complexes are more often trigonal bipyramidal.

The spin state of the metal atom in five-coordinate cobalt(II) and nickel(II) complexes is determined, to some extent, by the nature of the donor set[62b]. In general, combinations of four heavy donors (*e.g.* P, As, S, Se) give low spin, trigonal-bipyramidal Co^{II}, Ni^{II}, and Co^{I} complexes[61,62,63,81]. Ligands containing one or more nitrogen or oxygen donor groups give more variations in the magnetic ground state, the structure, and the number of polydentate ligand atoms actually bonded to the metal. A correlation between the spin state and the coordination geometry has been found for certain donor sets[62]. Cobalt(II) and nickel(II) complexes of the ligand (np_3) *(10)* shows just how sensitive the spin state is to changes in the donor set. For example, the $[CoX(np_3)]Y$ complexes (X = Cl or Br; Y = X, BF_4, PF_6, or BPh_4) are high-spin; NCS complexes and all iododerivatives, except for $Y = BPh_4$, are low-spin. In contrast, *all* the $[NiX(np_3)]Y$ complexes are low-spin[90]. If the tripod ligand is changed to the tetraphosphane pp_3 *(11)* all of the Co^{II} and Ni^{II} complexes become low-spin. This results from the changing nature of the apical ligand: phosphorus is a softer donor (higher nucleophilicity constant[62b]) than nitrogen and tends to produce low-spin complexes. The same spin-state trend is shown also by the cobalt(I) complexes $[CoX(pp_3)]$ and $[CoX(np_3)]$, where the two compounds are on opposite sides of, but are close to, the magnetic crossover point[91].

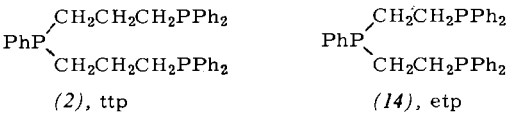
Attainment of the 18-valence-shell electronic configuration is also an important factor in determining the coordination number of phosphane complexes of metals in the latter half of the transition series[92,93]. This point is illustrated nicely by the structures of $[Pt^0(triphos)_2]$[10] and by the series $[M(NO)(np_3)]X$ (M = Fe, Co, Ni; X = I, NO_3, BF_4 or BPh_4)[94]. The platinum(0) complex has only four of the six phosphorus atoms bonded to the platinum[10]. In the nitrosyl series, the iron complex has a trigonal-bipyramidal geometry, whereas the cobalt and nickel complexes are tetrahedral, the central nitrogen atom of the ligand in these two cases being non-coordinated[94].

Stabilization of unusual metal oxidation states can be achieved relatively easily with polydentate phosphane ligands. For example, interesting tetrahedral nickel(I), d^9, and cobalt(I), d^8, complexes of general formula [MX(triphos)] are obtained when the metal salts are reduced with $NaBH_4$ in the presence to the [MI(triphos)] complexes. In the absence of a coordinating anion, the "tripod-like" symmetry of this triphosphane ligand leads to binuclear hydride complexes of type *(13)*[96].



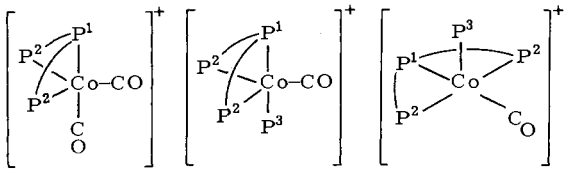
(13), M = Fe^{II}, Co^{II}

One can modify the coordination stereochemistry for a given donor set (*e.g.* P_3X_2) around a metal ion simply by changing the number of methylene groups in the connecting chains of a polyphosphane ligand. Such a study with the flexible ligands *(14)* (etp) and *(2)* (ttp) permitted the effect of the chelate ring size on the preferred structure of some five-coordinate cobalt(I) complexes to be determined[79]. The details of the stereochemistry and exchange processes for the complexes $[Co(CO)_2(etp)]X$, $[Co(CO)_2(ttp)]X$, $[Co(CO)(etp)L]X$ and $[Co(CO)L(ttp)]X$ ($X = BF_4$ or PF_6; $L = P(OMe)_3$, PPh_2H, PPh_2Me, PEt_3, or PPh_3) depend on



(2), ttp *(14)*, etp

both the monodentate ligand and on the triphosphane ligand. For example, the $[Co(CO)(etp)L]^+$ and $[Co(CO)_2(etp)]^+$ complexes are trigonal-bipyramidal with the equatorial positions occupied by a carbonyl ligand and the two terminal phosphorus atoms (P^2) of the triphosphane ligand; the axial positions are occupied by the central phosphorus atom (P^1) of the triphosphane and either a carbonyl *(15)* or a monophosphane ligand (P^3) *(16)*[79,97]. The monocarbonyl $[Co(CO)L(ttp)]^+$ complexes have square-pyramidal structures with L at the axial position. The change from square-pyramidal coordination geometry in $[Co(CO)\{P(OMe)_3\}(ttp)]^+$ *(17)* to



(15) *(16)* *(17)*

trigonal-bipyramidal in $[Co(etp)\{P(OMe)_3\}_2]^+$ can be attributed to the decrease in chelate bite angle of the ligand *(14)* (etp). As a consequence of the smaller bite angle in 5-membered chelate rings, the central phosphorus atom must either be pulled in abnormally close to the metal in a square-pyramidal geometry or be free to adopt a different coordination geometry where the central phosphorus atom is more equivalent to those of the terminal phosphorus atoms (P^2), *e.g.* as in the trigonal-bipyramidal geometries *(15)* and *(16)*.

The stereochemistry[98–103] and intramolecular exchange processes[98,102,103] of a number of five-coordinate complexes of cobalt(I) have been investigated. The preferred geometry in most cases appears to be based on a trigonal-bipyramid[98,99,104], although square-pyramidal complexes are also known[100,105]. With monodentate ligands, there are only small energy differences between the two limiting structures for d^8 pentacoordinate complexes[98]; in addition, structures intermediate between the idealized trigonal-bipyramidal and square-pyramidal structures are fairly common. Polyphosphane ligands can increase the intramolecular rearrangement energy sufficiently to freeze the exchange of phosphorus nuclei on the NMR time scale. Whereas, monodentate PR_3 and $P(OR)_3$ ligands produce non-rigid cobalt(I) complexes, the $[Co(CO)L(etp)]^+$ cations (L = a monodentate PR_3 or $P(OR)_3$ ligand) are stereochemically rigid in solution at room temperature[79]. One can obtain more detailed stereochemical information on the complexes from the P—P coupling constants than is possible with fluxional complexes of similar types of monodentate ligands.

The reduced dissociation tendency of chelating polyphosphane ligands permits synthesis of mixed d^{10} complexes of the type [M(triphosphane)(monophosphane)] (M = Ni^0, Pd^0, and Pt^0)[106]. Structural information and inferences regarding the hybridization around the metal can be obtained from the ^{31}P-NMR data. The Pt—P coupling observed for the triphosphane ligand *(12)* (triphos) in the [Pt(triphos)(monophosphane)] complexes decreases systematically from 3098 ± 2.4 to 2867 ± 2.4 Hz as the electronegativity of the monodentate phosphane changes from PPh_3 to PF_3, whereas the Pt—P coupling for the monodentate phosphane increases rapidly in the series PPh_3 (5400 Hz) < $P(OCH_2)_3CCH_3$ (6787 Hz) < $P(OPh)_3$ (9150 Hz) < PF_3 ($\approx$9500 Hz)[106]. The large difference in Pt—P coupling constants observed in the Pt(triphos)PR_3 complexes must be related to differences in the two types of Pt—P bonds, in particular to significantly different values of α^2_{Pt} in the expression for the Fermi contact term. As the triphosphane ligand limits expansion of the P—Pt—P angles to about 93—95°[107–111], those three Pt—P bonds will have a smaller s-character than "tetrahedral" Pt—P bonds; the remaining Pt—P bond will be hybridized to include more s-character and exhibits a larger coupling constant.

Complexes of polyphosphane ligands illustrate, finally, a control on the coordination behavior of ambidentate ligands such as the thiocyanate ion. Many different monodentate ligands have been used to determine the factors that influence the ambidentate nature of the SCN^- ion, but the relative importance of σ-bonding, π-bonding, or steric effects of the ancillary ligands is still unresolved in detail[112]. The uncertainty remains because it is impossible to change the electronic effects of substituents on donor atoms over a wide range independently of steric effects. The three closely related chelating ligands *(18)*, *(19)* and *(20)* were used to define a *cis*-arrangement of two thiocyanate ligands in the palladium(II) complexes, to have a 90° P—Pd—L angle within the chelate ring,

$Me_2PCH_2CH_2CH_2NMe_2$ *(18)*

$Me_2PCH_2CH_2CH_2PMe_2$ *(19)*

$Me_2PCH_2CH_2CH_2AsMe_2$ *(20)*

and to have a dimethylphosphino-ligand common to all three complexes[113]. In dichloromethane solution, the nitrogen and arsenic derivatives give *(18)* and *(19)* complexes containing *both* N- and S-bonded thiocyanate groups, while both thiocyanate groups are N-bonded in the case of the diphosphane ligand. If one makes the reasonable assumption that the NMe_2 and $AsMe_2$ groups are not effective π-acceptors, these "mixed" thiocyanate complexes are apparently consistent with the argument that the phosphane group is a good π-acceptor; thus it should influence the *trans*-thiocyanate group to be N-bonded[112]. However, strong phosphorus σ-bonding *via* p-orbitals would also favor a N-bonded thiocyanate group *trans* to the phosphorus atom, as we have discussed above.

The structure of [Pd(SCN)(NCS)L], where L is $Ph_2PCH_2CH_2CH_2NMe_2$, is shown in Figure 5a[114]. The structure has the N-bonded thiocyanate *trans* to P and the S-bonded thiocyanate *trans* to N. This case does not distinguish between the σ- *vs* π-bonding nature of phosphorus, however, as both effects give the same result here. In an effort to control the donor properties of the bidentate ligand, *Meek* and *Li* prepared a series of palladium thiocyanate complexes containing the three chelating diphosphane ligands $Ph_2P(CH_2)_nPPh_2$, where $n = 1$, 2, and 3[113b,115]. All three ligands contain equivalent donor groups, and Figures 5b—5d show the remarkable trend that was found in the structures

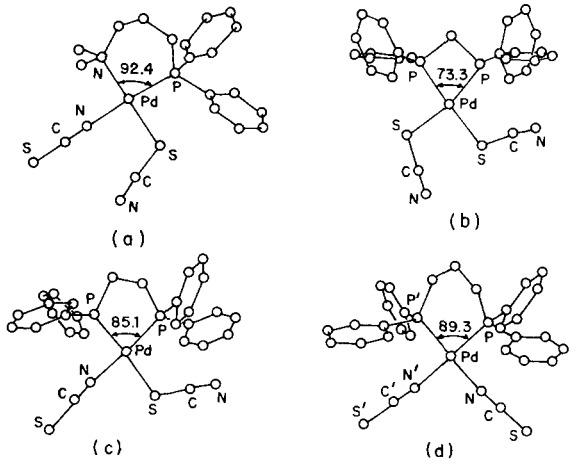
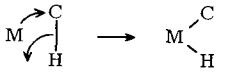


Fig. 5. Perspective drawings of the molecular structures of: (a) $Pd(SCN)(NCS)(Ph_2PCH_2CH_2CH_2NMe_2)$; (b) $Pd(SCN)_2(Ph_2PCH_2PPh_2)$; (c) $Pd(SCN)(NCS)(Ph_2PCH_2CH_2PPh_2)$; and (d) $Pd(NCS)_2(Ph_2PCH_2CH_2CH_2PPh_2)$.

of the three palladium thiocyanate complexes, namely, that the mode of thiocyanate bonding changes from S,S for $n=1$, to S,N for $n=2$, to N,N for $n=3$ as the chelate P—Pd—P angle increases from 73.3 to 89.3°[115,116]. These angular changes are easily interpreted in terms of increasing steric effects adjacent to the thiocyanate groups as the chain length between the phosphorus atoms increases. The regular change in the bonding mode of the thiocyanate ion is explicable in terms of steric effects, without involking any π-bonding arguments.

5. Some Reactions of Coordinated Tertiary Phosphane Complexes

The metallation of carbon-hydrogen and phosphorus-carbon bonds of coordinated tertiary phosphane ligands is an important example of intramolecular oxidative addition reactions which have implications for mechanistic proposals in homogeneous and heterogeneous catalysis[117]. A number of possible mechanisms of oxidative addition exist[118] but, in general, and in the particular context of the metallation of carbon-hydrogen bonds, a coordinatively unsaturated species is obviously necessary. As was anticipated some time ago[43], the carbon-hydrogen bond must be in close proximity to the metal, the geometry being such as to encourage speculation of a concerted three center addition mechanism such as

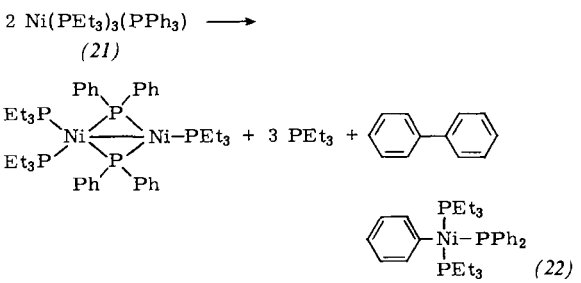


Sterically demanding phosphanes provide readily, as we have noted, for coordinatively unsaturated species and may often force a carbon-hydrogen bond into a suitable precursor state prior to metallation. The subtlety of steric control of metallation is illustrated by the reactions of $[PtCl_2(PhCN)_2]$ with tertiary phosphanes: with di-*tert*-butyl(neopentyl)phosphane, the neopentyl group is readily metallated but with di-*tert*-butyl(*n*-propyl)phosphane, L, a simple mixture of *cis*- and *trans*-complexes, $[PtCl_2L(PhCN)]$, is produced[119]. No metallated product was formed from the slightly more crowded complex, $[PtCl_2(t\text{-}BuCN)\{P(t\text{-}Bu)_2(n\text{-}Pr)\}]$ although the dimeric complex $[Pt_2Cl_4\{P(t\text{-}Bu)_2(n\text{-}Pr)\}_2]$ undergoes slow hydrogen-deuterium exchange, at the 3-position of the *n*-propyl group in strong acid media[120]; this exchange appears to be regiospecific with the concomitant suggestion that the reaction proceeds *via* a cyclometallated species, perhaps similar to the binuclear complex formed from the metallated neopentylphosphane.

Although the geometries of non-primary valence interactions of carbon-hydrogen bonds with metals and of cyclometallated species are well known, the precise nature of the interactions and of the mechanistic details of the oxidative addition remain uncertain. A quasi-covalent view of the interactions imagines that the carbon-hydrogen σ-bond is a two-electron donor in a polycentric interaction with the electron-deficient metal. Tertiary phosphane complexes of palladium(0), platinum(0), rhodium(I), and palladium(II), for example, achieve an eighteen-electron configuration for the metal if this kind of accountancy is adopted. No phosphane complexes demonstrate the strong interactions observed in pyrazolyl borate complexes of molybdenum[121], where the carbon-hydrogen-metal bonds (M...H ≈ 2.1 Å) are competitive energetically with metal-olefin bonds. With the longer M...H 'bonds' of 2.5 to 2.7 Å in tertiary phosphane complexes, it is presumably more appropriate to think of the interaction as predominantly an electrostatic one, which could still be sufficient to satisfy the electrostatic potential requirements of the metal[29].

So far as electronic effects in cyclometallation are concerned, it is apparent—albeit from, as yet, limited data—that both electrophilic and nucleophilic pathways may be followed[122]. The ease of cyclometallation is dependent upon the metal basicity[123] and, in essence, its electron density as determined by the Lewis acid-base properties of the remaining ligands in the coordination sphere, a feature well illustrated by the varied reactions of $[IrClL_3]$ (L = *para*-substituted arylphosphanes), complexes which have interest in their catalytic dehydrogenation reactions[124].

Insertion of metals into phosphorus-carbon bonds of coordinated tertiary phosphanes remains largely at a descriptive stage. The stability of binuclear and polynuclear μ-phosphido complexes of d^8 and d^9 systems obviously contributes to the cleavage process. Refluxing of $[IrH(CO)(PPh_3)_3]$ in *n*-heptane gives $[Ir(CO)PPh_3(\mu\text{-}PPh_2)_2]_2$, a complex with a metal-metal bond length of 2.55 Å and a formal metal-metal double bond[125]. Triosmium complexes with μ-phosphido, μ-phenyl and μ-dehydrobenzene ligands have been characterized from the reaction of dodecarbonyltriosmium with triphenylphosphane[126,127]. Many other examples of oxidative-addition reactions presented by $Os_3(CO)_{12}$ have been described subsequently and used to suggest the proposition that reactions of organometallic clusters may be similar to those at surfaces

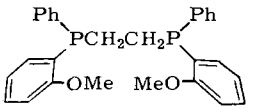


of transition metals[128, 129]. A satisfying study of phosphorus-carbon bond cleavage is the recent one by *Fahey* and *Mahan*[130]: the reaction of the nickel complex *(21)* is assumed to proceed *via* the intermediate *(22)*, through a reversible oxidative addition of the metal to triphenylphosphane.

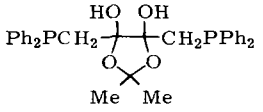
6. Outlook

Our discussion has not suggested that metal to phosphorus π-bonding is nonexistent; rather that its importance in determining equilibrium molecular parameters may have been overemphasized in the past. Further correlations of bond geometries with metal-phosphorus coupling constants and, where appropriate, with ESR data should limit further the remaining ambiguities of interpretation. The cone angle concept could undoubtedly be extended in its utility by realistic molecular mechanics calculations while SCF calculations of the relation between chelate ring sizes and conformations and imposed metal coordination geometries could provide for more sophisticated ligand design.

This article reflects the activity, during the past decade, in four areas of the chemistry of the later transition metals; an obvious growth area is that of asymmetric synthesis *via* homogeneous catalysis[131–133]. Impressive results have been obtained with complexes of *P,P'*-bis(*o*-methoxyphenyl)-*P,P'*-diphenylethylenediphosphane *(23)*, a ligand which is chiral



(23)



(24)

at both phosphorus atoms[134]. The catalyst is uniquely effective in the homogeneous hydrogenation of α-acylaminoacrylic acids. High optical purities can be obtained also with catalysts which are not chiral at phosphorus but have a chiral substituent; examples are rhodium(I) complexes of the diphosphane, 4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolan-4,5-diol *(24)* (DIOP), which are useful for asymmetric hydrogenation and hydrosilylation reactions[135].

A final note is necessary by way of recognizing evidence that tertiary phosphane complexes of the earlier transition metals, particularly molybdenum and tungsten, are providing much interest in connection with their activation of dinitrogen[136, 137] and carbon-hydrogen bonds[138]. It may be here that polydentate phosphane ligands will be particularly important in such chemical reactions by controlling preferred electron configurations and geometries of coordinatively unsaturated species.

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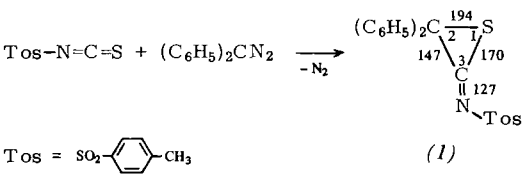
Communications are brief preliminary reports of research work in all areas of chemistry which, on account of its fundamental significance, novelty, or general applicability, should be of interest to a broad spectrum of chemists. Authors of communications are requested to state reasons of this kind justifying publication on submission of their manuscript. The same reasons should be clearly apparent from the manuscript. In cases where the editorial staff decide, after due consultation with independent referees, that these conditions are not met, manuscripts will be returned to the authors with the request to submit them for publication in a specialist journal catering for scientists working in the field concerned.

A Stable Thiiranimine[**]

By *Gerrit L'abbé, Jean-Paul Dekerk, Jean-Paul Declercq, Gabriel Germain*, and *Maurice Van Meerssche*[*]

Aziridinimines are known[1] and a successful synthesis of a stable oxiranimine has been claimed recently[2]. The sulfur analogs, thiiranimines, have not yet been reported, although many examples of their open-chain dipolar isomers have been isolated[3], and both the ring-closed and open-chain forms have been postulated as reactive intermediates[4]. In principle, thiiranimines would be accessible from the thermal interaction of diazoalkanes with isothiocyanates, but all the publications on the subject only report the formation of the aromatic 1,2,3-thiadiazoles[5]. We describe here the first synthesis and characterization of such a species.

When equimolar amounts of tosyl isothiocyanate and diphenyldiazomethane are allowed to react in anhydrous ether at 0°C, nitrogen evolution occurs and at the end of the reaction *(1)* is isolated in 67% yield upon cooling of the solution to a low temperature. In addition, a small amount (*ca.* 1%) of 4,4-diphenyl-5-tosylimino-1,2,3-trithiolane (structure determined by X-ray analysis), m. p. 186–187°C, is also obtained from the residue by column chromatography on silica gel with benzene/ethyl acetate (95:5) as the eluant.



(1)

The new three-membered ring *(1)* exhibits IR (KBr) absorptions at 1700(m) and 1630 cm^{-1} (s), while in the ^{13}C-NMR spectrum ($CDCl_3$) the ring-carbon absorptions are found at $\delta = 46.5$ (sp^3-*C*) and 170.7 ppm (*C*=N). The result of an X-ray structure analysis[6] is shown in Figure 1.

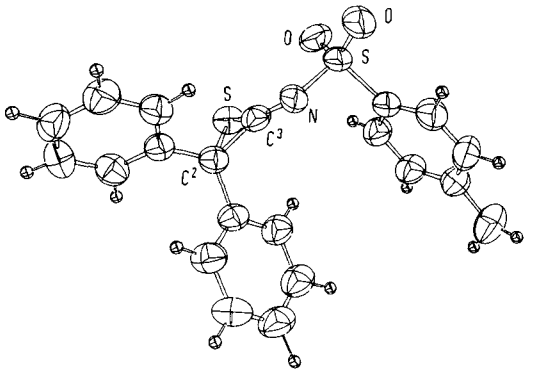
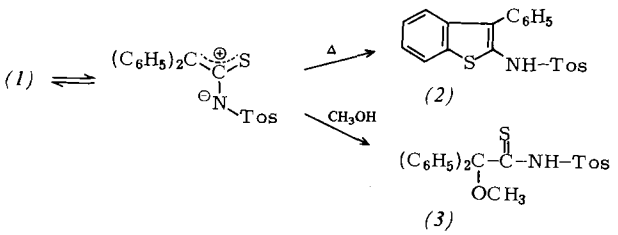


Fig. 1. Molecular structure of thiiranimine *(1)* in the crystalline state.

The thiirane ring features a large S—C^2 distance (194 pm compared with 181 pm for the sum of the covalent radii) and short C^2—C^3 (147 pm) and S—C^3 (170 pm) bonds; a situation also observed for α-lactams[7] and diaziridinimines[8]. The exocyclic C=N bond has a normal length of 127 pm[9], and the tosyl group is located in the *cis* position with respect to the C^3—S bond (*Z* isomer). The internal ring angles are 47.2° (at S), 58.1° (at C^2), and 74.7° (at C^3). As expected, the four atoms, S, C^2, C^3 and N are almost coplanar.



In its chemical reactions, *(1)* is cleaved at the unusually long S—C^2 bond. Thus, when a chloroform solution of *(1)* is allowed to stand at room temperature for 3 d, the benzo[*b*]-thiophene *(2)*, m.p. 55–56°C, is obtained in quantitative yield. The latter is also formed as side product during the synthesis of *(1)* if the reaction is carried out, or the product worked up, without cooling. Methanolysis of *(1)* furnishes *(3)* as yellow crystals, m.p. 128–130°C in quantitative yield. The structures *(2)* and *(3)* were assigned on the basis of elemental analysis and spectral evidence.

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CAS Registry numbers:
(1), 65665-36-3; *(2)*, 65665-37-4; *(3)*, 65665-38-5; tosyl isothiocyanate, 1424-52-8; diphenyldiazomethane, 883-40-9; 4,4-diphenyl-5-tosylimino-1,2,3-trithiolane, 65665-39-6

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[**] *J.-P. Dekerk* and *J.-P. Declercq* are indebted respectively to the I. W. O. N. L. and the F. N. R. S. (Belgium) for a fellowship. Financial support from the Ministry of National Education is gratefully acknowledged.

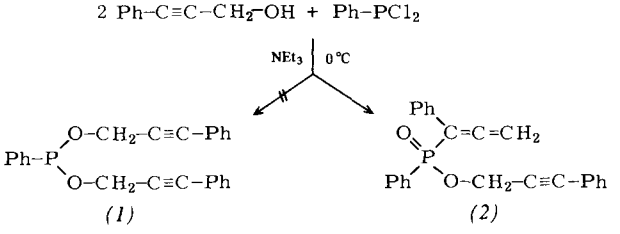
[1] *H. Quast, E. Schmitt*, Angew. Chem. *82*, 395 (1970); Angew. Chem. Int. Ed. Engl. 9, 381 (1970); *H. Quast, L. Bieber, ibid. 87*, 422 (1975) and *14*, 428 (1975), respectively; *H. Quast, P. Schäfer*, Tetrahedron Lett. *1977*, 1057.
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[5] *B. Eistert, M. Regitz, G. Heck, H. Schwall* in Houben/Weyl: Methoden der organischen Chemie, Vol. X/4. Thieme, Stuttgart 1968, pp. 785–786.
[6] Monoclinic crystals, space group $P2_1/n$, $Z=4$, $a=2065.0(7)$, $b=815.3(4)$, $c=1109.1(5)$ pm, $\beta=90.52(3)°$. A total of 2480 independent reflections were measured (Syntex diffractometer, $Cu_{K\alpha}$ radiation, $2\theta_{max}=114°$), 1894 were considered as observed. Structure solved with the MULTAN 77 program and refined with X-Ray 72 to an R factor of 0.05 [*P. Main, L. Lessinger, M. M. Woolfson, G. Germain, J. P. Declercq*, MULTAN 77, a System of Computer Programmes for the Automatic Solution of Crystal Structures from X-ray Diffraction Data, York (U. K.) and Louvain-la-Neuve (Belgium), 1977; *J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, S. R. Hall*, X-ray System. Tech. Rep. TR-192, Computer Science Center, University of Maryland, 1972].
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Intramolecular Cycloaddition of a "P=O-Activated" Acetyleneallene Derivative[**]

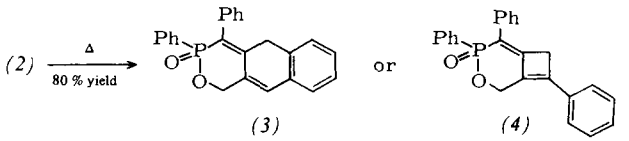
By *Werner Winter, Albert Scheller, Thomas Butters*, and *Walter Holweger*[*]

In an attempt to synthesize the phosphonous diester *(1)* from 3-phenyl-2-propyn-1-ol and dichloro(phenyl)phosphane, instead of obtaining the desired product we isolated the phosphinate *(2)* [column chromatographic purification, yield 65%, yellowish oil; IR: 2250 (C≡C stretching), 1950 and 1920 (typical for allenes), 1220 (P=O), 1020 cm^{-1} (P—O—C); $^{31}P\{^1H\}$-NMR: $\delta=-32.5$ (H_3PO_4 ext., CH_2Cl_2, 36.43 MHz); ^{1}H-NMR: $\delta=7.1$–8.0 (m, 15 arom.H), 5.03 (d, $J_{PH}=21$ Hz, P—OCH_2), 5.00 (s, =C=CH_2); MS: $m/e=370$ (M^+)].



As previous examples have shown, reaction of phosphorus(III) halides with α-hydroxyacetylenes leads to allenic phosphane oxides *via* nucleophilic attack of the phosphorus at the triple bond and subsequent propargyl rearrangement[1]; the formation of *(2)* can be explained analogously. The phosphinate *(2)* is unstable at room temperature and on standing transforms into a yellow strongly fluorescing crystalline isomer. In boiling toluene the transformation is already complete within 1 h. The spectroscopic data for the new compound [m.p. 215 °C; IR: 1195 cm^{-1} (P=O), no allene and acetylene bands; $^{31}P\{^1H\}$-NMR: $\delta=-21.4$ (H_3PO_4 ext., CH_2Cl_2); ^{1}H-NMR: $\delta=3.70$ (m, —CH_2—); 5.20 (m, P—OCH_2), 7.2—8.0 (m, 15 arom.H); ^{13}C-NMR: $\delta=37.4$ (d, —CH_2—, $^3J_{PC}\approx12$ Hz), 63.2 (d, P—OCH_2, $^2J_{PC}\approx8$ Hz), 127—132 (m, arom.C) TMS int.] are consistent with structures *(3)* and *(4)*.

The presence of a s-*trans*-1,4-diphenylbutadiene structural unit follows, above all, from the UV absorption maximum (335 nm, $\log\varepsilon=4.32$, EtOH), calculated according to the



Woodward-Fieser rules[2] to be 329 nm, both for *(3)* as well as *(4)*. Only the X-ray structural analysis[3] of the yellow crystals permits unequivocal decision in favor of structure *(4)* (cf. Fig. 1).

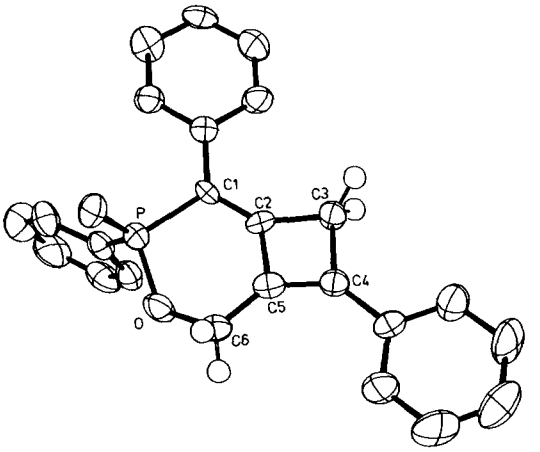
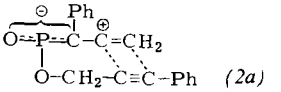


Fig. 1. ORTEP plot of the cycloaddition product *(4)*; the hydrogen atoms of the phenyl rings have been omitted for clarity. The bond lengths in the bicyclic skeleton are: P—C1 1.802(6), P—O 1.605(5), C1—C2 1.35(1), C2—C3 1.54(1), C3—C4 1.55(1), C4—C5 1.36(1), C5—C6 1.48(1), C5—C2 1.46(1), and C6—O 1.49(1) Å.

To our knowledge, the formation of 4-oxo-4,5,8-triphenyl-3,4λ^5-oxaphosphabicyclo[4.2.0]octa-5,8-diene *(4)* constitutes the first example of a spontaneous cycloaddition of non-perhalogenated acetyleneallene components and is reminiscent of the cycloaddition of ketenes with olefins[4].

We assume that the reaction *(2)* → *(4)* is a $[2_s+2_a]$ process on the basis of the following findings: a) the course of the reaction is largely independent of the polarity of the solvent, b) the bonding in the allene moiety of *(2)* appears to resemble that in the active vinylium form of ketenes[5] if a "P=O activated" resonance structure *(2a)* is assumed,



(2a)

and c) in the educt *(2)*, the steric conditions prerequisite for an orthogonal proximation of the terminal allene double bond to the triple bond are optimally fulfilled.

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CAS Registry numbers:
PhC≡CCH_2OH, 1504-58-1; $PhPCl_2$, 644-97-3; *(2)*, 65465-75-0; *(3)*, 65465-76-1; *(4)*, 65465-77-2

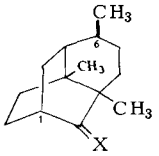
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[+] Author to whom correspondence should be addressed.
[**] This work was supported by the Deutsche Forschungsgemeinschaft.

[1] Cf. *H. G. Viehe* in: The Chemistry of Acetylenes. Marcel Dekker, New York 1969, pp. 388ff.
[2] *R. B. Woodward*, J. Am. Chem. Soc. *64*, 72, 76 (1942); *L. F. Fieser, M. Fieser, S. Rajagopalan*, J. Org. Chem. *13*, 800 (1948).
[3] Monoclinic, space group C2/c; $a=27.11$, $b=7.45$, $c=18.65$ Å, $\beta=90.81°$; $Z=8$; 1408 symmetry independent reflections [$I\geq2\sigma(I)$], Nonius CAD-4, $Mo_{K\alpha}$, graphite monochromator; solution: direct methods (program by *G. M. Sheldrick*, Cambridge); refinement: $R=0.069$ (P, O, C anisotropic).
[4] Cf. *D. Seebach* in Houben-Weyl: Methoden der organischen Chemie, Vol. IV/4. Thieme, Stuttgart 1971, p. 136.
[5] *R. B. Woodward, R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. Int. Ed. Engl. *8*, 781 (1969).

Divinyl Ketone as Michael Acceptor

By *Dietrich Spitzner*[*]

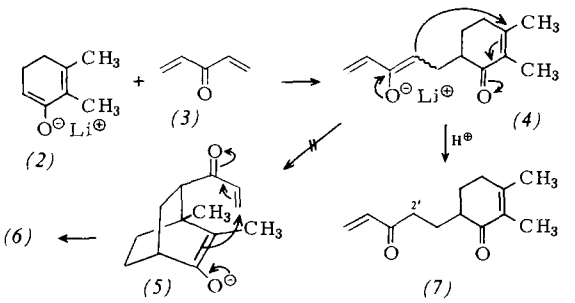
In the course of our investigations on the synthesis of tricyclic sesquiterpenes such as seychellene *(1)* we attempted the preparation of the closely related compound 3,8-dimethyltricyclo[5.3.1.$0^{3,8}$]undecan-2,6-dione *(6)* in one operation *via* three consecutive Michael additions.



(1), X = CH_2
(6), X = O, O on C-6 instead of CH_3 and H

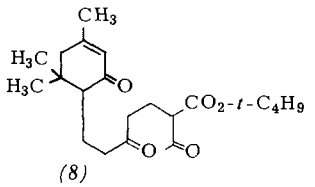
In view of the previous finding that a cyclohexadienolate of type *(2)*, generated under kinetically controlled conditions, reacts with acrylates *via* double Michael addition to give 5-oxobicyclo[2.2.2]octane-2-carboxylates[1], we used instead of an acrylate the potentially divalent Michael acceptor divinyl ketone *(3)*[2].

It is known[3] that in the aprotic Michael addition, polymerization proceeds much faster than the addition reaction with the desired donor. Nevertheless, we obtained a 1:1 adduct (EI-MS: $m/e = 206$, M^+) of *(2)* and *(3)*. Both the IR spectrum [film; 3100 (C=CH_2), 1670 cm^{-1} (enone)] as well as the 270-MHz ^{1}H-NMR spectrum[4] [$CDCl_3$; $\delta = 6.40$—5.81 (ABX, vinyl), 2.72 (t, 2'-H), 2.36 (br. s), 1.89 (br. s, CH_3), 1.75 (br. s, CH_3), several multiplets between 2.36 and 1.55] and especially the ^{13}C-NMR spectrum[4] [$CDCl_3$; $\delta = 200.4$ (two CO groups distinguishable only on addition of Yb(fod)$_3$); 153.6, 136.3, 130.2, 127.8 (olefinic C); 44.6 (CH); 37.0, 31.5, 27.8, 24.3, (CH_2); 21.0, 10.8 (CH_3)] afford proof of formation of *(7)*, *i.e.* that only the first of the three possible additions takes place. Intramolecular secondary additions leading to *(6)* do not occur.



While *(3)* is capable of undergoing double Michael addition under the usual conditions, it reacts with anions such as *(2)* as monovalent acceptor under aprotic conditions, and thus proves to be a possible C-5 synthon for terpene and steroid syntheses. By way of example, an adduct analogously synthesized from *(3)* and isophorone reacts regioselectively with *tert*-butyl acetoacetate under conventional protonic conditions to give the monoadduct *(8)* (55.6 %), which after hydrolysis and decarboxylation can be subjected to further aldol condensation[5].

Trialkylsilyl groups in the α-position[3] of *(3)* should have a pronounced effect on the course of this aprotic Michael addition.



(8)

Experimental:

A solution of *(3)* (1.3 equiv.) in THF is added dropwise at −70 °C in the presence of an inert gas to a tetrahydrofuran solution of *(2)*, prepared from 2,3-dimethyl-2-cyclohexene *(9)* and lithium isopropyl(cyclohexyl)amide[1] (molar ratio 1:1.1). The mixture is stirred at this temperature for 15 min and then neutralized with 1 N HCl and extracted with ether. The oil obtained after drying and concentration of the organic phase is distilled in a bulb tube: After removal of forerunnings (mainly unreacted *(9)*), *(7)* distils over at 90—110 °C/0.03 torr as a pale yellow oil (18 %) which crystallizes on storage in an ice-box.

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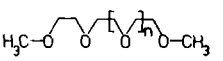
CAS Registry numbers:
(2), 65636-27-3; *(3)*, 1890-28-4; *(7)*, 65636-28-4; *(8)*, 65636-29-5; *(9)*, 1122-20-9

[1] *R. A. Lee*, Tetrahedron Lett. *1973*, 3333.
[2] *H. A. P. de Jongh, H. Wynberg*, Recl. Trav. Chim. Pays-Bas *82*, 202 (1963).
[3] *R. K. Boeckman, Jr.*, J. Am. Chem. Soc. *96*, 6179 (1974); *G. Stork, J. Singh, ibid. 96*, 6181 (1974).
[4] I thank Priv.-Doz. *G. Höfle*, Berlin, for recording the ^{13}C- and ^{1}H-NMR spectra.
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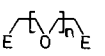
Complexes of Short-Chain Oligo(ethylene Glycol Ethers) Bearing only *One* Rigid Donor End Group[**]

By *Ulrich Heimann* and *Fritz Vögtle*[*]

While simple oligo(ethylene glycol dimethyl ethers) such as pentaglyme *(1)*, $n = 3$, are reported[1] not to form crystalline complexes with salts of alkali and alkaline earth metals[2], such complexes are readily obtained with "noncyclic crown ethers" *(2)*, $n \geq 1$, which are rendered rigid by aromatic donor end groups (E)[3].

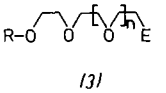


(1)



(2)

This communication considers whether *a single* donor end group E suffices to permit isolation of crystalline complexes of alkali metal ions. If this is the case, the next question to be answered concerns the minimum length of the oligo(ethylene glycol ether) chain in the limiting case.



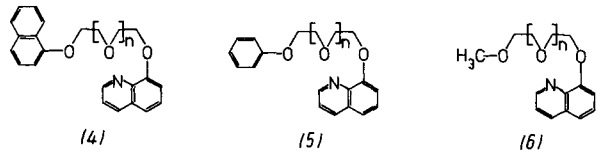
(3)

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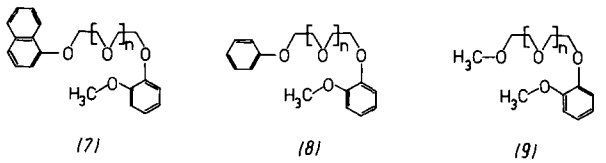
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[**] Work supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

We found that one end of the oligo ether chain may exhibit less donor strength if the other donor end group E is a strong coordinating one. Thus, in the case of tetra- and hexa-dentate neutral ligands *(4)–(6)* with an 8-quinolyloxy group at one end of the chain and a 1-naphthyloxy, phenoxy, or even methoxy group at the other end, we still obtained crystalline complexes with a series of salts (Table 1). Just one effective end group was also sufficient to permit isolation of crystalline alkali metal ion complexes in the case of *(7)–(9)*.



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



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

The chain segment adjacent to E can enclose the cation in a planar fashion; a second donor end group is apparently not required[4] for formation of crystalline complexes but can nevertheless exert a stabilizing action and, above all, raise the complexation constant[5].

Table 1. Ligands synthesized and their complexes with alkali metal salts.

Ligand [a]	Chain length *n*	Complex [a, b] with	Stoichiometry	m. p. [°C]
(4a)	2	$NaClO_4$	1:1	130–131
(4b)	3	KSCN	1:1	152
(5a)	2	$NaClO_4$	1:1	124–125
(5b)	3	KSCN	1:1 [c]	91– 92
(6a)	1	NaSCN	1:1	142
(6b)	2	$NaClO_4$	1:1	116–118
(6c)	3	KSCN	1:1	88–90
(7a)	2	[d]		
(7b)	3	$NaClO_4$	1:1	99–100
(8a)	2	[d]		
(8b)	3	$NaClO_4$	1:1	73–74
(9a)	2	[d]		
(9b)	3	$NaClO_4$	1:1	102

[a] Correct analytical data and/or high resolution mass spectra were obtained for all ligands and complexes.
[b] All complexes are colorless.
[c] Also contains 0.5 mol of H_2O.
[d] Alkali metal salts complexed; however no simple stoichiometry between ligand and salt could be detected.

Comparison of the ^{1}H-NMR spectra of the naphthol ether *(4a)* and the phenol ether *(5a)* provides information about the arrangement of the ends of the chain carrying no donor group in the complex: while a large upfield shift of the α- and β-quinoline protons is observed on transition from the free ligand to the complex in the case of *(4a)*, only the α-quinoline proton exhibits an upfield shift in the complex of *(5a)*. Since spatial proximity can be assumed between the quinoline and the naphthalene ring and the benzene ring, respectively, the difference can be interpreted as due to the larger anisotropic region of the naphthalene ring. The mutual orientation of the chain ends in the novel complexes and the arrangement of the central ion and the donor centers are being examined by means of X-ray structure analysis[4].

It is possible, by variation of the donor end group E and of the lipophilic chain end, to construct a whole series of ligand/complex topologies. These systems permit almost continuous variation of the balance between lipophilic and hydrophilic properties, and of complex stability constants and complexation kinetics[6]. Such versatility is significant for some potential applications[7].

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CAS Registry numbers:
(4a), 65496-10-8; *(4b)*, 65496-11-9; *(5a)*, 65496-12-0; *(5b)*, 65496-13-1; *(6a)*, 57310-80-2; *(6b)*, 65496-14-2; *(6c)*, 65496-15-3; *(7a)*, 65496-16-4; *(7b)*, 65496-17-5; *(8a)*, 65496-18-6; *(8b)*, 65545-78-0; *(9a)*, 65496-19-7; *(9b)*, 65496-20-0

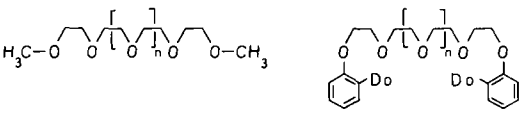
Table 1, complexes from top to bottom:
65504-68-9; 65504-70-3; 65504-72-5; 65504-74-7; 65504-76-9; 65504-78-1; 65504-80-5; 65504-82-7; 65504-84-9; 65504-86-1

[1] *C. J. Pedersen*, J. Am. Chem. Soc. *89*, 2495, 7017 (1967).
[2] Nor had we hitherto made such an observation in numerous complexation experiments with noncyclic neutral ligands [3].
[3] *E. Weber, F. Vögtle*, Tetrahedron Lett. *1975*, 2415; *F. Vögtle, H. Sieger*, Angew. Chem. *89*, 410 (1977); Angew. Chem. Int. Ed. Engl. *16*, 396 (1977); *W. Rasshofer, F. Vögtle*, Chem. Ber. *111* (1978), in press; *W. Rasshofer, G. Oepen, F. Vögtle, ibid. 111*, 419 (1978).
[4] X-Ray structure analyses of selected complexes are in progress: Prof. Dr. *W. Saenger et al.*, Göttingen.
[5] Cf. *H. Sieger, F. Vögtle*, Angew. Chem. *90*, *212* (1978); Angew. Chem. Int. Ed. Engl. *17*, 198 (1978).
[6] Survey: *B. Tümmler, G. Maass, E. Weber, W. Wehner, F. Vögtle*, J. Am. Chem. Soc. *90*, 4683 (1977).
[7] Cf. *J. G. Schindler, R. Dennhardt, W. Simon*, Chimia *31*, 404 (1977); *J. G. Schindler*, Biomed. Tech. *22*, 235 (1977).

Alkaline Earth Metal Complexes of Simple Oligo(ethylene Glycol Ethers)[**]

By *Heinz Sieger* and *Fritz Vögtle*[*]

This study of the relation between structure and complexation of simple neutral ligands was instigated by the following observations: a) glyme compounds of type *(1)* do not form[1] crystalline alkali metal ion complexes and b) "noncyclic crown ethers" *(2)* bearing rigid donor end groups (Do = donor center in the end group) readily form such complexes[1].

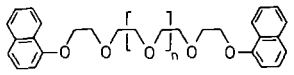


(1) *(2)*

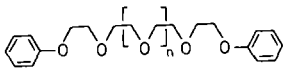
The key question arising from X-ray structure comparisons of several complexes of ligands *(2)*[2] is: how short can the chain be and what is the minimum donating ability of the chain ends required for oligo(ethylene glycol ethers) to still just form crystalline complexes with alkali or alkaline earth metal salts?

Careful crystallization experiments showed that the polyethers *(3)* and *(4)* bearing two donor-free but rigid aryl groups at their ends and containing *at least five* ether oxygen atoms ($n \geq 1$) gave crystalline complexes, especially with alkaline earth metal ions. Some of the complexes, including the alkali metal ion complex of *(3c)*, are listed in Table 1.

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[**] Supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



(3)



(4)

Table 1. Crystalline alkaline earth and alkali metal ion complexes of the oligo(ethylene glycol ethers) synthesized [6].

Ligand [a]	Abbreviation	Complex [a] with	Stoichiometry [b]	m. p. [°C]
(3a)	$O_5(Naph)_2$	$Ca(SCN)_2 \cdot 4\,H_2O$	[c]	163
(3b)	$O_6(Naph)_2$	$Ba(SCN)_2 \cdot 2\,H_2O$	1:1:1	120
(3c)	$O_7(Naph)_2$	$NaClO_4$	1:1	111
(3d)	$O_8(Naph)_2$	$Ba(SCN)_2 \cdot 2\,H_2O$	1:1:1	117
(4a)	$O_6(Ph)_2$	$Ba(SCN)_2 \cdot 2\,H_2O$	$1:1:\frac{1}{2}$	138–141
(4b)	$O_7(Ph)_2$	$Ba(SCN)_2 \cdot 2\,H_2O$	$1:1:\frac{1}{2}$	135
(4c)	$O_8(Ph)_2$	$Ba(SCN)_2 \cdot 2\,H_2O$	1:1	111–115
(5a)	$O_7(Me)_2$	$Ba(SCN)_2 \cdot 2\,H_2O$	1:1	141–142
(5b)	$O_8(Me)_2$	$Ca(SCN)_2 \cdot 4\,H_2O$	1:2:1	160 (dec.)

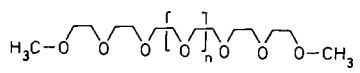
[a] Correct analytical data and/or high resolution mass spectra were obtained for all ligands and complexes.
[b] Ligand: salt: H_2O.
[c] This recrystallizable complex gives reproducible values on elemental analysis from which no simple stoichiometry can be deduced.

If the oligooxaalkane chain in *(3)* and *(4)* is shortened to only four oxygen atoms ($n=0$) no crystalline complexes are obtained—in accord with *Pedersen*'s findings[5a].

Solid/liquid phase transfer of permanganate and liquid/liquid phase transfer of picrate[3] by ligands with donor-free chain ends in organic phases is considerably less pronounced than in the case of ligands *(2)* having two donor end groups. A corresponding effect is noted with the complex stabilities of the neutral ligands *(3)* and *(4)*[4].

Formation of a pseudocyclic compound or a helix during complexation of the weak ligands *(3)* and *(4)* in solution can be deduced from the upfield shift of the signals of the aromatic and aliphatic protons in the ^{1}H-NMR spectrum ($CDCl_3$). With a sufficiently long chain (six CH_2CH_2O units) the complexation is recognizable only from the upfield shift of the aliphatic CH_2 groups.

Encouraged by the discovery that short-chain oligo(ethylene glycol diaryl ethers) *(3)* and *(4)* ($n \geq 1$) form crystalline alkaline earth metal ion complexes, we examined complex formation with the well known oligo(ethylene glycol dimethyl ethers) *(1)* (glymes)[3]. In spite of repeated attempts[5], no crystalline complexes of alkali and alkaline earth metal ions could so far be isolated. It is therefore highly surprising that we have now obtained crystalline complexes of heptaglyme and even hexaglyme [with $Ca(SCN)_2$ and $Ba(SCN)_2$]; relevant data are listed in Table 1.



(5)

Although they have low complexation constants, the oligo(ethylene glycol diaryl and dialkyl ethers) *(3)*, *(4)*, and *(5)* are of interest *e.g.* for microelectrode systems[1] owing to their expected high selectivity[4] towards ions of alkali and alkaline earth metals. The ligands *(3)*–*(5)* indicate a borderline of complexation as regards crystallization of the complexes; however, they also number among the simplest ligand systems on reducing the chain length. Isolation of the new complexes shows that glymes not only "interact" with solvents and cations (solvation-association effects)[3] but also form defined complexes whose study seems to be fundamental.

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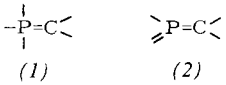
CAS Registry numbers:
(3a)·$Ca(SCN)_2$, 65545-40-6; *(3b)*·$Ba(SCN)_2$, 65545-38-2; *(3c)*·$NaClO_4$, 65545-36-0; *(3d)*·$Ba(SCN)_2$, 65545-34-8; *(4a)*·$Ba(SCN)_2$, 65545-32-6; *(4b)*·$Ba(SCN)_2$, 65545-30-4; *(4c)*·$Ba(SCN)_2$, 65545-28-0; *(5a)*·$Ba(SCN)_2$, 65545-26-8; *(5b)*·$Ca(SCN)_2$, 65545-24-6

[1] Cf. *U. Heimann, F. Vögtle*, Angew. Chem. *90*, 211 (1978); Angew. Chem. Int. Ed. Engl. *17*, 197 (1978); and references cited therein.
[2] *W. Saenger, H. Brand, B. S. Reddy, I. H. Suh, G. Weber*, to be published.
[3] Review: *F. Vögtle, E. Weber*, Kontakte (Merck) *2/77*, 16.
[4] Concerning the complex stability of oligo(ethylene glycol ethers) in solution, see [3] and *G. Chaput, G. Jeminet, J. Juillard*, Can. J. Chem. *53*, 2240 (1975); *U. Takaki, J. Smid*, J. Am. Chem. Soc. *96*, 2588 (1974); *E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, Th. C. Tarnowski, St. S. Moore, D. J. Cram, ibid. 99*, 2564 (1977); *B. Tümmler, G. Maass, E. Weber, W. Wehner, F. Vögtle, ibid. 99*, 4683 (1977).
[5] a) *C. J. Pedersen*, J. Am. Chem. Soc. *89*, 2495, 7017 (1967); b) *R. J. Levins*, Anal. Chem. *43*, 1045 (1971); c) *E. Weber, F. Vögtle*, Tetrahedron Lett. *1975*, 2415.
[6] *Note added in proof* (February 9, 1977): Meanwhile, we have also obtained the complex $O_5(Ph)_2 \cdot Ba(SCN)_2 \cdot 1\,H_2O$, mp. 85 °C (dec.).

Novel Diylides Containing Tricoordinate Phosphorus[**]

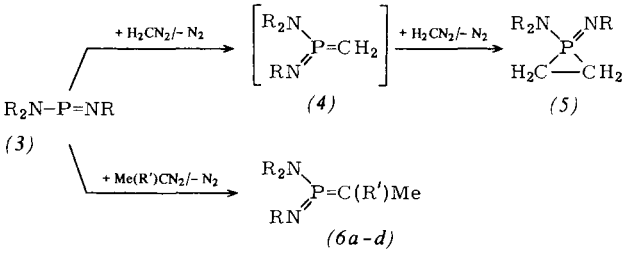
By *Edgar Niecke* and *Dirk A. Wildbredt*[*]

In contrast to the classical phosphorus ylides, the methylenephosphoranes *(1)*, compounds of tricoordinate λ^5-phosphorus containing a PC double bond[1] *(2)* have hitherto only been postulated as unstable intermediates[2].



(1) (2)

Thus the intermediacy of the methylenephosphorane *(4)* in the reaction of bis(trimethylsilyl)aminotrimethylsilyliminophosphane *(3)* with diazomethane was suggested merely by orientionally specific cycloaddition to form the λ^5-phosphirane *(5)*[2b]. We have now been able to isolate the homologous aminoiminomethylenephosphoranes *(6a–d)* by subjecting α-alkylated diazoethanes to this reaction.



R = $SiMe_3$
R' = Me*(a)*, CH_2Me*(b)*, $CHMe_2$*(c)*, CMe_3*(d)*

The new compounds *(6)* of tricoordinate λ^5-phosphorus with two different ylidic centers are colorless thermally stable liquids which are largely resistant to atmospheric moisture.

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[**] Part 15 of Studies on Phosphazenes of Coordination Number 2 and 3. This work was supported by the Fonds der Chemischen Industrie. – Part 14: *E. Niecke, R. Kröher, S. Pohl*, Angew. Chem. *89*, 902 (1977); Angew. Chem. Int. Ed. Engl. *16*, 864 (1977).

Their composition and structure in the gaseous and liquid phase have been confirmed by elemental analysis, mass spectrometry[3], and NMR data (Table 1)[4].

Table 1. ^{31}P-, ^{1}H-, and ^{13}C-NMR data of the iminomethylenephosphoranes *(6a–d)* [a].

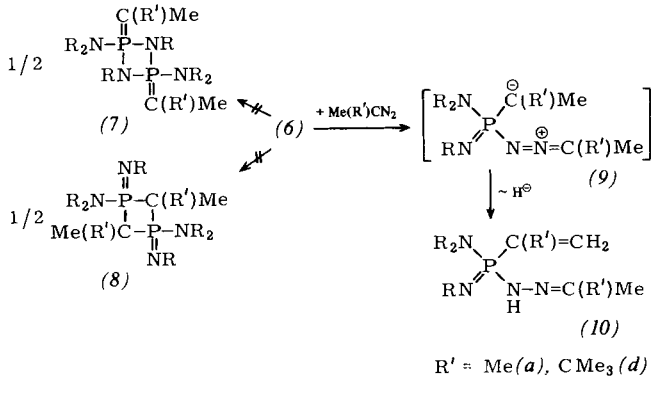
R′	Me	CH_2Me [b]	$CHMe_2$ [b]	CMe_3 [b]
$\delta^{31}P$	86.4	83.9	83.1	75.4
$\delta^{1}H$ (J_{HP}[Hz])				
$PNSiMe_3$	0.05 (0.55)	0.05 (0.55)	0.04 (0.55)	0.04 (0.55)
$PN(SiMe_3)_2$	0.31 (0.10)	0.30 (0.10)	0.31 (0.10)	0.31 (0.10)
PCMe	1.69 (27.7)	1.66 (28.0)	1.59 (28.6)	1.69 (29.2)
PCR′	1.80 (28.4)	2.23 (26.5)	3.09 (20.5)	
		0.98 (0.5)	1.02 (0.5)	1.22 (0.6)
$\delta^{13}C$ (J_{CP}[Hz])				
$PNSiC_3$	3.55 (3.1)	3.35 (3.1)	3.32 (3.0)	3.36 (2.7)
$PN(SiC_3)_2$	2.32 (2.2)	2.34 (2.0)	2.29 (2.2)	3.38 (2.1)
PC	77.40 (215.9)	84.12 (210.3)	88.10 (207.4)	88.91 (214.0)
PCMe	18.80 (13.7)	16.59 (13.2)	11.37 (12.7)	16.47 (15.2)
PCR′	19.70 (12.5)	25.72 (13.1)	29.00 (13.6)	34.67 (9.7)
		14.17 (14.2)	21.69 (13.5)	30.71 (11.0)

[a] 30% solution in CH_2Cl_2 (^{31}P, ^{1}H) or 60% solution in $CDCl_3$ (^{13}C), with H_3PO_4 as external (^{31}P) or TMS as internal standard (^{1}H, ^{13}C), 25°C. [b] On the basis of the rotational barriers of the PC double bonds, positional isomers are present in the ratios 2:1 *(6b)*, 5:1 *(6c)*, >10:1 *(6d)*; the reported data apply to the preferred isomer.

The coordination number 3 at the phosphorus atom is apparent from the downfield shift of the ^{31}P-NMR signal on going from *(1)* to *(6)* and the deshielding of the ^{31}P nucleus as compared with correspondingly substituted bis(imino)phosphoranes (δ = 45–55)[5].

In the ^{1}H- and $^{13}C\{^{1}H\}$-NMR spectra[6], the signals of the trimethylsilylimino group and of the methylene carbon atom exhibit double splitting as a result of interaction with only one phosphorus atom. Noteworthy is the chemical shift for the sp^2-hybridized carbon (δ value *ca.* 80), which indicates a lower electron density at the carbanionic center [(p–p)π bonding contribution] of *(6)* compared with that of *(1)*. Owing to the different hybridization of the phosphorus atom in *(6)* and in *(1)* it cannot be said how reliably the large magnitude of $^{1}J_{CP}$ (>200 Hz) can be regarded as indicating only slight polarity of the phosphorus-carbon double bond.

Examination of molecular models underlines the importance of steric effects in the stabilization of coordinatively unsaturated phosphorus in *(6)*; such effects also explain the kinetic inhibition of the [2+2] cycloadditions *(6)*→*(7)* and *(6)*→*(8)*. Steric constraints likewise preclude a [2+1] cycloaddition on further reaction with diazoalkane in analogy to *(4)*→*(5)*. Instead, the adduct *(10)* is formed; the iminophosphoranes *(10a,d)*[7] may be formed from the intermediate zwitterions *(9a,d)*.



Experimental

A solution of diazoalkane $Me(R')CN_2$[8] [*(a)–(c)* in diethyl ether, *(d)* in tetrahydrofuran] cooled to −40°C is added dropwise to ice-cooled, stirred bis(trimethylsilyl)aminotrimethylsilyliminophosphane *(3)* (8.0 g, 29 mmol) until the reaction solution turns pink. Stirring is continued for 1 h at room temperature, the solvent is removed *in vacuo*, and the residue purified by fractional distillation. The procedure yields 7.5 g (80%) of *(6a)*, 5.0 g (55%) of *(6b)*, 8.5 g (85%) of *(6c)*, or 8.3 g (80%) of *(6d)*.

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(3), 50732-21-3; *(6a)*, 65496-09-5; *(6b)*, 65496-08-4; *(6c)*, 65496-07-3; *(6d)*, 65496-06-2; *(10d)*, 65496-05-1; *(10d)*, 65496-04-0; Me_2CN_2, 2684-60-8; $Me(CH_2Me)CN_2$, 65496-03-9; $Me(CHMe_2)CN_2$, 65496-02-8; $Me(CMe_3)CN_2$, 65496-01-7; ^{13}C, 7440-44-0

[1] Compounds of the methylenephosphane type are known: *G. Becker*, Z. Anorg. Allg. Chem. *423*, 242 (1976).
[2] a) *M. Regitz*, Angew. Chem. *87*, 259 (1975); Angew. Chem. Int. Ed. Engl. *14*, 222 (1975) and references cited therein; b) *E. Niecke, W. Flick*, *ibid. 87*, 355 (1975) and *14*, 363 (1975), respectively.
[3] MS (70eV) in *m/e*: *(6a)* M^+ 320 (24%), *(6b)* M^+ 334 (17%), *(6c)* M^+ 348 (14%), *(6d)* M^+ 362 (15%); *(6a–d)* $M^+ - CH_3$ (100%).
[4] The unchanged Raman spectrum at −130°C proves the existence of monomeric species in the solid state.
[5] *E. Niecke, O. J. Scherer*, Nachr. Chem. Tech. *23*, 395 (1975); *E. Niecke, W. Flick, H. G. Schäfer*, unpublished.
[6] We are grateful to Prof. Dr. *H. Lackner*, Universität Göttingen, for recording the ^{13}C-NMR spectra.
[7] *(10a)*: b.p. 79–80°C/0.1 torr; IR: νNH = 3320, $\nu_{as}CH_2$ = 3090, νC=C = 1638, νP=N = 1345 cm^{-1}; $\delta^{31}P$ = 1.6; $\delta^{1}H$ = 5.17, 5.26 ($PCCH_2$), $^{3}J_{HP}$ = 43.2, 19.7 Hz, $^{gem}J_{HH}$ = 2.7 Hz.
(10d): m. p. 55–58°C; IR: νNH = 3280, $\nu_{as}CH_2$ = 3085, νC=C = 1615, νP=N = 1338 cm^{-1}; $\delta^{31}P$ = −5.8; $\delta^{1}H$ = 4.41, 4.53 ($PCCH_2$), $^{3}J_{HP}$ = 34.1, 33.9 Hz, $^{gem}J_{HH}$ = 1.8 Hz.
[8] The diazoalkanes $Me(R')CN_2$ *(b–d)*, which, to our knowledge, have not previously been reported, were prepared from the corresponding hydrazones by oxidation with HgO [R′ = CH_2Me, $CHMe_2$] or by vacuum pyrolysis of the *N*-lithio-*N*-tosylhydrazone [R′ = CMe_3] according to *G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, H. Shechter*, J. Am. Chem. Soc. *87*, 935 (1965).

Use of the "Zip" Reaction for the Synthesis of a 53-Membered Polyaminolactam[1]

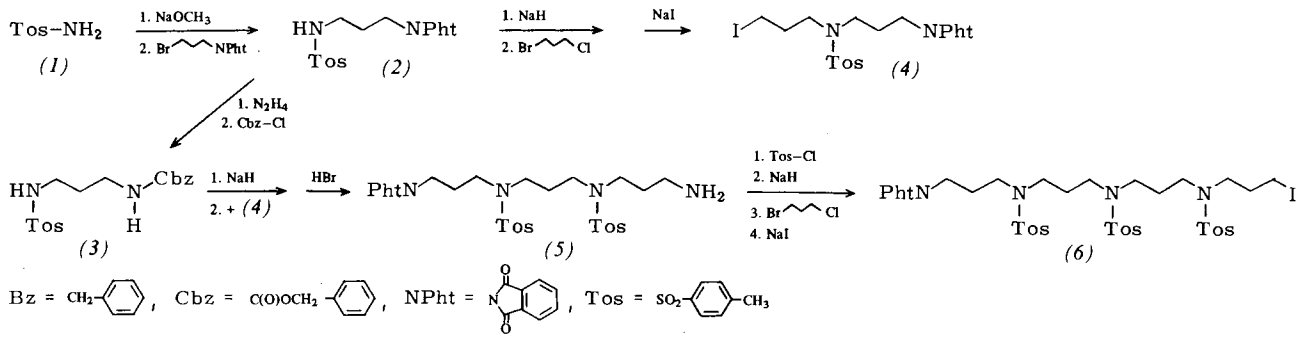
By *Urs Kramer, Armin Guggisberg, Manfred Hesse*, and *Hans Schmid* (deceased)[*]

We recently reported the ring expansion of a 13-membered lactam with a 3-aminopropyl substituent linked to nitrogen to give a 17-membered aminolactam[2]. If two such ring-expansion units combined as 7-amino-4-azaheptyl substituent are linked to the nitrogen atom, ring expansion to a 21-membered diaminolactam is possible[2]. In order to check whether this reaction can be generalized—*i.e.* whether any desired number of ring-expansion units linked together can be used for the construction of even larger rings—we chose as our new goal the synthesis of the 53-membered ring *(11)*. Other than in previous experiments (stepwise method: repeated addition of acrylonitrile followed by catalytic hydrogenation)[2] we decided to use the "fragment condensation method". As primary building block we used *(6)*, prepared according to Scheme 1: Alkylation of the sodium salt of *p*-toluenesulfonamide *(1)*

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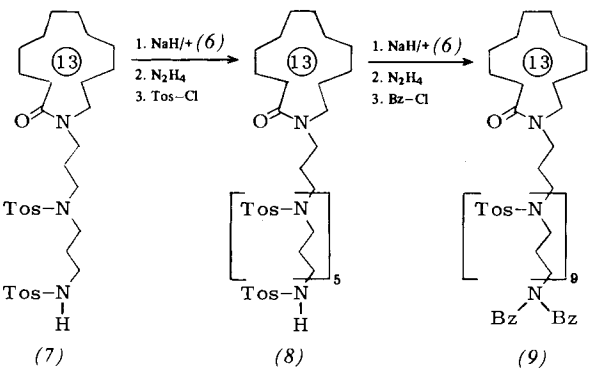
with *N*-(3-bromopropyl)phthalimide affords the trimethylenediamine derivative *(2)* (55 % yield). *(2)* can be converted, on the one hand, into 7-iodo-1-phthalimido-4-tosyl-4-azaheptane *(4)* (79 %) by alkylation with 1-bromo-3-chloropropane/NaH and subsequent treatment with NaI, or on the other, into *(3)* (71 %) by hydrazinolysis and benzyloxycarbonylation. Coupling of *(3)* and *(4)* with NaH and cleavage of the benzyloxycarbonyl group with HBr/glacial acetic acid affords *(5)* (96 %), whose tosylation, alkylation with 1-bromo-3-chloropropane/NaH and subsequent treatment with NaI leads to the 15-iodo-1-phthalimido-4,8,12-tritosyl-4,8,12-triazapentadecane *(6)* in 87 % yield.

Scheme 1



The previously reported[3] ditosyllactam derivative *(7)* can be alkylated with *(6)* (Scheme 2), and on subsequent hydrazinolysis and tosylation is converted into *(8)* (61 %). Further alkylation, of the sodium salt of *(8)*, with *(6)* yields a nonatosylphthalimide, whose molecular weight has been determined by addition (alkali-metal ion) field desorption mass spectrometry[4a] to be $[M+Na]^+ = 2310 \pm 6$ (calcd. 2306)[4b,c]. Hydrazinolysis and benzylation [phase transfer reaction: benzyl chloride and benzyl(trimethyl)ammonium hydroxide in H_2O/CH_2Cl_2] of this intermediate affords the derivative *(9)* (68 %). Electrolytic detosylation[5] of *(9)* to the *N*,*N*-dibenzylamine (FD-MS of the hydrochloride: $[M+1]^+ = 948$[4c]) and subsequent hydrogenolysis yields 1-(39-amino-4,8,12,16,20,24,28,32,36-nonaazanonatriacontyl)-1-azacyclotridecan-2-one *(10)* (FD-MS of the free base: $[M+1]^+ = 768$[6]).

Scheme 2



Treatment of *(10)* with potassium (3-amino)propylamide/1,3-diaminopropane (KAPA[7]; 45 min) and acidic workup leads to the 1,5,9,13,17,21,25,29,33,37,41-undecaazatripentacontan-42-one *(11)* in 38 % yield (Scheme 3); FD-MS of the hydrochloride: $[M+1]^+ = 768$[4c], of the *N*-decaacetyl compound: $[M+Na]^+ = 1210$[6]; total yield of *(11)* w.r.t. *(2)*: 7.5 %. The low yield of the last step compared to other transamidation reactions[2] is due to the formation of side-products in the transamidation[3,8] and losses during purification of the extremely polar reaction product.

The above compounds were characterized by IR and mass spectra [*(1)* to *(5)*, *(7)*, *(8)*] and, in part, by ^{1}H-NMR spectra; their purity was confirmed by TLC and elemental analysis.

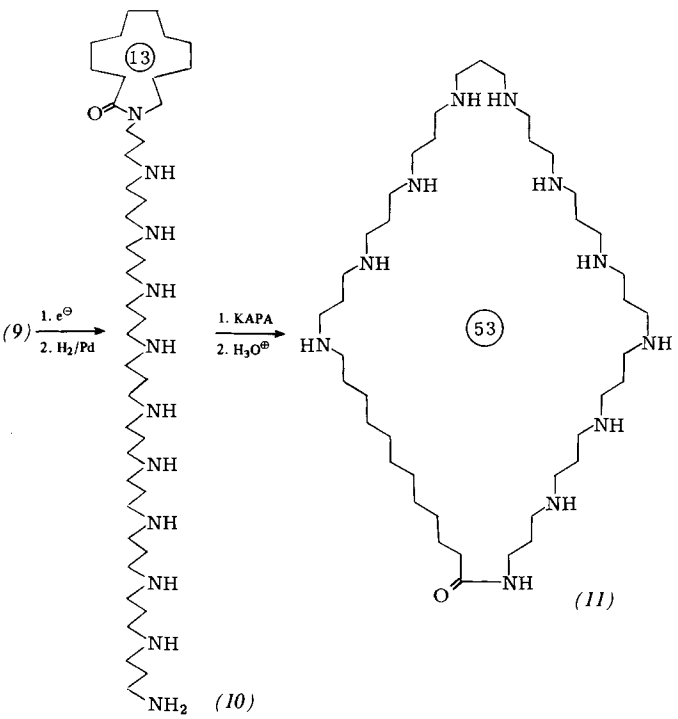
The macrocycle *(11)* differs from the isomeric educt *(10)* in its spectroscopic and TLC properties in the same way as the structurally related 21- and 33-membered polyaminolactams differ from their isomeric precursors[2,9]:

a) In the TLC analysis [silica gel (Merck); $CHCl_3/CH_3OH$/25 % ammonia = 3:5:3] a larger R_f value is found for *(11)* than for *(10)*, while the corresponding *N*-acetyl derivatives show exactly the opposite chromatographic properties ($CHCl_3/CH_3OH = 1:1$).

b) In the Fluram test[10] for primary amines, *(10)* shows a strong bright green fluorescence at 360 nm, while *(11)*, containing only secondary amino groups, does not fluoresce.

c) The IR spectrum ($CHCl_3$) of *(10)* is characterized by a band at 1620 cm^{-1} (*N*,*N*-disubstituted amide), that of *(11)* by amide I and amide II bands at 1660 and 1515 cm^{-1} (*N*-monosubstituted).

Scheme 3



As could be shown in investigations on model compounds[3], the transamidation of *(10)* to *(11)* proceeds as a "zip" reaction[2], *via* stepwise attack of a *N,N*-disubstituted amine nitrogen at the lactam carbonyl carbon, with successive formation and opening of a six-membered ring, and ring expansion by four members. The end product is the resonance stabilized amide anion (with enclosure of the terminal amino group). Our findings show that the "zip" reaction can be used for the synthesis of macrocycles of any desired size containing the structural element $-(CH_2)_3-N-$.

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(1), 70-55-3; *(2)*, 38353-77-4; *(3)*, 17415-89-3; *(4)*, 65545-56-4; *(5)*, 65545-57-5; *(6)*, 65545-58-6; *(7)*, 65545-59-7; *(8)*, 65605-32-5; *(9)*, 65605-33-6; *(10)*, 65605-34-7; *(11)*, 65545-60-0; *N*-(3-bromopropyl)phthalimide, 5460-29-7; 1-bromo-3-chloropropane, 109-70-6

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Anodic NN Linkage by Oxidation of Anions of Primary and Secondary Amines[**]

By *Reinhold Bauer* and *Hartmut Wendt*[*]

The preparation of hydrazine or substituted hydrazines by anodic oxidation of ammonia or alkyl- and aryl-amines usually gives only very poor yields. The reason for this is that hydrazines are generally more readily oxidized than amines and are therefore largely decomposed if formed at the anode.

Grinstead[1] has shown that anodic oxidation of the imidodisulfate ion affords the hydrazinetetrasulfonate ion.

We have now found that amide ions *(1)* can be oxidized at potentials that lie about 1 V lower than those of amines. Pertinent data are listed in Table 1, which also shows that the anodic halfwave potential of the tetraalkylhydrazines *(3a)* lies between those of the corresponding amines and amide ions. This is one of the conditions for preparation of hydrazines by anodic oxidation of amine anions.

The anodic polarograms of the amide ions *(1)* reveal irreversible 1e steps. This suggests that anodic oxidation of *(1)* generates the aminyl radicals *(2)*, which then dimerize to the hydrazines *(3)*.

$$\underset{(1)}{R^1R^2N^{\ominus}} - e^{\ominus} \longrightarrow \underset{(2)}{R^1R^2N^{\bullet}} \qquad \begin{matrix}(a)\text{: } R^1 = R^2 = \text{Alkyl} \\ (b)\text{: } R^1 = \text{Alkyl},\ R^2 = H\end{matrix}$$

$$2\ R^1R^2N^{\bullet} \longrightarrow \underset{(3)}{R^1R^2N{-}NR^2R^1}$$

Potentiostatically controlled oxidation of lithium dibutylamide at Pt anodes in tetrahydrofuran does indeed produce tetrabutylhydrazine in 45% current yield (cf. Table 2).

Table 1. Anodic halfwave potentials of primary and secondary alkylamines and their anions in tetrahydrofuran at C electrodes ($E_{1/2}$ [mV] *versus* saturated calomel electrode).

R^1	R^2	R^1R^2NH	R^1R^2NLi	$R^1R^2NNR^2R^1$
n-C_4H_9	H	+1150	−160	—
cyclo-C_6H_{11}	H	+1260	+ 50	—
t-C_4H_9	H	+1210	− 95	—
n-C_4H_9	n-C_4H_9	+ 940	−120	+300

Table 2. NN coupling products on anodic oxidation of anions of primary and secondary amines.

R^1	R^2	Product	Anode potential [a] [mV]	Yield [b] [%]
n-C_4H_9	H	Azobutane	+300	33 (38)
cyclo-C_6H_{11}	H	Azocyclohexane	+300	23 (26)
t-C_4H_9	H	2,2'-Azoisobutane	+300	25 (31)
n-C_4H_9	n-C_4H_9	Tetrabutylhydrazine	+ 50	38

[a] *Versus* aqueous saturated calomel electrode.
[b] Yields after workup; values in parentheses determined by gas chromatography (3% SE-30 on Varaport 30).

In contrast, the anions of primary alkylamines *(1b)* yield the azoalkanes *(4)*. We explain this observation by assuming that the hydrazines *(3b)* which have lower pK values than the amines are transformed, in the presence of excess amide ions, into the readily oxidizable hydrazide ions and thence oxidized to the azoalkanes *(4)*.

$$2\ RHN^{\ominus} - e^{\ominus} \longrightarrow 2\ RHN^{\bullet} \longrightarrow \underset{(3b)}{RHN{-}NHR}$$

$$(3b) + RHN^{\ominus} \longrightarrow RHN{-}NR^{\ominus} + RH_2N$$

$$RHN{-}NR^{\ominus} - 2\ e^{\ominus} + RHN^{\ominus} \longrightarrow \underset{(4)}{RN{=}NR} + RH_2N$$

Experimental

The anodic syntheses are performed under N_2 as protective gas.

Lithium cyclohexylamide (0.02 mol), prepared in a divided electrolysis cell with a Pt anode and a Pt cathode by reaction of cyclohexylamine with an equivalent amount of n-butyllithium at −30°C, is electrolyzed in an electrolyte consisting of anhydrous tetrahydrofuran (100 ml) and lithium perchlorate (5.3 g) at −10°C at a controlled potential (Table 2). After consumption of 0.04 F the solution is neutralized with acetic acid and, after removal of solvent, azocyclohexane is isolated from polymeric products and supporting electrolyte by extraction with n-hexane. Purification is accomplished by column

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chromatography on Al_2O_3. The procedure affords 0.22 g (23%) of azocyclohexane, m. p. 33–34 (literature value[2] 34.5 °C), which is identified by gas chromatography and comparison of its IR, ^{1}H-NMR, and mass spectra with those of a product prepared from *N,N'*-dicyclohexylsulfamide[3].

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(1a), 65545-75-7; *(1b)*, R' = *n*-C_4H_9, 62063-13-2; *(1b)*, R' = *cyclo*-C_6H_{11}, 65545-76-8; *(1b)*, R' = *t*-C_4H_9, 54448-42-9; *(2a)*, 51770-69-5; *(2b)*, R' = *n*-C_4H_9, 51770-68-4; *(2b)*, R' = *cyclo*-C_6H_{11}, 65545-77-9; *(2b)*, R' = *t*-C_4H_9, 41084-93-9; *(3a)*, 60678-70-8; *(4)*, R' = C_4H_9, 2159-75-3; *(4)*, R' = *cyclo*-C_6H_{11}, 2159-74-2; *(4)*, R' = *t*-C_4H_9, 927-83-3

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Triazene Transfer with Activated 2-Tetrazenes[1]

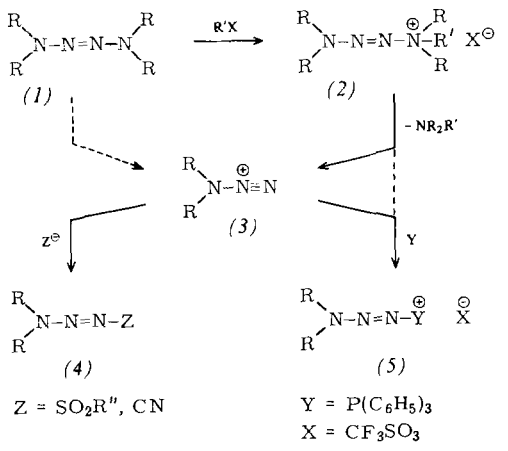
By *Ernst Stöldt* and *Richard Kreher*[*]

Tetraalkyl-2-tetrazenes *(1)*[2], which exhibit relatively high thermal stability, fragment in the presence of electrophiles [protic and Lewis acids, triethyloxonium and nitrosyl tetrafluoroborate[3a], alkylating and acylating reagents, ketenes, and isocyanates[3b]]. Electrophilic attack at the terminal dialkylamino group leads to an activated onium intermediate *(2)* from which the positively charged leaving group and the preformed N_2 molecule are generally eliminated. Intermediate formation of *N*-diazonium ions *(3)* should be detectable by competitive trapping reactions with nucleophiles[4]. The preparative consequence of this reaction sequence is transfer of a triazene group by activated 2-tetrazenes *(2)*.

Electrophilic alkylation of tetramethyl-2-tetrazene *(1)*, R = CH_3, affords isolable pentaalkyltetrazenium salts *(2)* with R' = CH_3, C_2H_5. Reaction with methyl iodide gives crystalline *(2a)*[5] whose structure was established by analysis and spectroscopy. Replacement of the halogen atom by the complex tetraphenylborate anion gives a relatively stable tetrazenium salt *(2b)*, while the explosive salt *(2c)* is formed with triethyloxonium tetrafluoroborate. Considerable advantages are offered by methylation of the tetrazene *(1)* with methyl trifluoromethanesulfonate to give the spectroscopically characterized trifluoromethanesulfonate *(2d)*, which can be used directly for triazene transfer.

The reaction of pentaalkyltetrazenium salts *(2)* with anionic nucleophiles [Z = arenesulfinate] always leads to exchange of the trialkylammonium group. This provides a preparative entry to sulfonyltriazenes *(4)*[6]; the reaction with cyanide proceeds analogously to give 1-cyano-3,3-dimethyltriazene *(4)*, Z = CN. These transformation products result formally from a coupling reaction of the *N*-diazonium ion *(3)* with the anionic nucleophile. Available evidence is insufficient for an unequivocal decision between the mechanistic alternatives—two-step S_N reaction of the activated tetrazenium ion *(2)* or dissociation reaction *via* the electrophilic intermediate *(3)*.

On reaction of *(2)* with neutral nucleophiles [triphenylphosphane], replacement of the trialkylammonium group affords the remarkably stable onium salts *(5)*; the triazene structure is again retained. An analogous transfer reaction is possible with the tetrazene *(1)* after activation with acetyl chloride.



2-Tetrazenium salts *(2)*, R = CH_3 [8]

(2a), R' = CH_3 and X = I, yield 60%, m.p. 64–65 °C (dec.) (precipitated from *n*-pentane); ^{1}H-NMR ($CDCl_3$, −30 °C): τ = 6.35 (s, CH_3), 6.40 (s, $3CH_3$), 6.77 (s, CH_3).—*(2b)*, R' = CH_3 and X = $(C_6H_5)_4B$, yield 62%, m.p. 89–91 °C (dec.) (ethanol, ether); ^{1}H-NMR (CD_3NO_2, −5 °C): τ = 2.63 (mc, 8CH aromatic), 3.02 (mc, 12CH aromatic), 6.57 (s, CH_3), 6.83 (s, $3CH_3$), 6.90 (s, CH_3).—*(2c)*, R' = C_2H_5 and X = BF_4, yield 57%, m.p. 34–35 °C (dec.) (dichloromethane); ^{1}H-NMR ($CDCl_3$, −30 °C): τ = 6.27 (q, *J* = 7.5 Hz, NCH_2), 6.41 (s, CH_3), 6.69 (s, $2CH_3$), 6.78 (s, CH_3), 8.61 (t, *J* = 7.5 Hz, CCH_3).—*(2d)*, R' = CH_3 and X = CF_3SO_3, explosive decomp. at *ca.* 0 °C; ^{1}H-NMR ($CDCl_3$, −40 °C): τ = 6.45 (s, CH_3), 6.63 (s, $3CH_3$), 6.83 (s, CH_3).

1-Arenesulfonyl-3,3-dimethyltriazenes *(4)*, R = CH_3 and Z = SO_2R''

(4a), R'' = C_6H_5, yield 78%, m.p. 89 °C (ethanol); ^{1}H-NMR ($CDCl_3$): τ = 2.08 (mc, 2CH aromatic), 2.47 (mc, 3CH aromatic), 6.44 (s, CH_3), 6.78 (s, CH_3).—*(4b)*, R'' = *p*-$CH_3C_6H_4$, yield 92%, m.p. 145–146 °C (ethanol); ^{1}H-NMR ($CDCl_3$): τ = 2.19 (d, *J* = 8.5 Hz, 2CH aromatic), 2.72 (d, *J* = 8.5 Hz, 2CH aromatic), 6.47 (s, CH_3), 6.82 (s, CH_3), 7.61 (s, CH_3).—*(4c)*, R'' = *p*-$NO_2C_6H_4$, yield 89%, m.p. 189–190 °C (dec.) (ethanol); ^{1}H-NMR ($CDCl_3$): τ = 1.70 (mc, 4CH aromatic), 6.36 (s, CH_3), 6.70 (s, CH_3).—*(4d)*, R'' = *p*-$CH_3OC_6H_4$, 50%, m.p. 121 °C (ethanol); ^{1}H-NMR ($CDCl_3$): τ = 2.15 (d, *J* = 9.0 Hz, 2CH aromatic), 3.03 (d, *J* = 9.0 Hz, 2CH aromatic), 6.13 (s, CH_3), 6.45 (s, CH_3), 6.79 (s, CH_3).—*(4e)*, R'' = *p*-$CH_3CO{-}NH{-}C_6H_4$, yield 78%, m.p. 181 °C (dec.) (methanol); ^{1}H-NMR (D_6-DMSO): τ = −0.25 (s, br, NH), 2.22 (s, 4CH aromatic), 6.45 (s, CH_3), 6.82 (s, CH_3), 7.89 (s, CH_3).

1-Cyano-3,3-dimethyltriazene

(4), R = CH_3 and Z = CN, yield 73%, m.p. 33 °C, (diethyl ether/*n*-pentane); ^{1}H-NMR ($CDCl_3$): τ = 6.33 (s, CH_3), 6.72 (s, CH_3); IR (film): $\tilde{\nu}$ = 2195 cm^{-1} (CN); UV (dichloromethane): λ_{max} = 268 nm ($\log\varepsilon$ = 4.14).

1-Triphenylphosphonio-3,3-dimethyltriazenetrifluoromethanesulfonate

(5), R = CH_3, yield 58%, m.p. 179–180 °C (ethanol); ^{1}H-NMR ($CDCl_3$): τ = 2.27 (mc, 15CH aromatic), 6.15 (s, CH_3), 6.33 (s, CH_3).

Triazene transfer can be accomplished directly with tetramethyl-2-tetrazene *(1)* on reaction with *p*-toluenesulfinic acid in a two-phase medium. An independent route to 3,3-dimethyl-1-tosyltriazene *(4b)* is opened by the reaction of diethyl phosphate *N',N'*-dimethylhydrazide with *N,N*-ditosylhydroxylamine[7] which can act as a nitrosation agent and as a precursor for arenesulfinate ions in the presence of triethylamine. This reaction scheme probably involves intermediates similar to those occurring in the transformation of activated tetrazenium ions *(2)*.

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The experimental results confirm the concept of detecting *N*-diazonium ions *(3)* by competitive reactions with nucleophiles but still have to be supplemented by kinetic measurements.

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(1), 6130-87-6; *(2a)*, 6669-81-4; *(2b)*, 65651-89-0; *(2c)*, 65651-91-4; *(2d)*, 65651-92-5; *(4a)*, 65651-93-6; *(4b)*, 25286-68-4; *(4c)*, 65651-94-7; *(4d)*, 65651-95-8; *(4e)*, 65651-83-4; *(4)*, R = CH_3, Z = CN, 65651-84-5; *(5)*, 65651-86-7; iodomethane, 74-88-4; methylium tetraphenylborate, 65701-71-5; ethylium tetrafluoroborate, 65651-87-8; methyl trifluoromethanesulfonate, 333-27-7

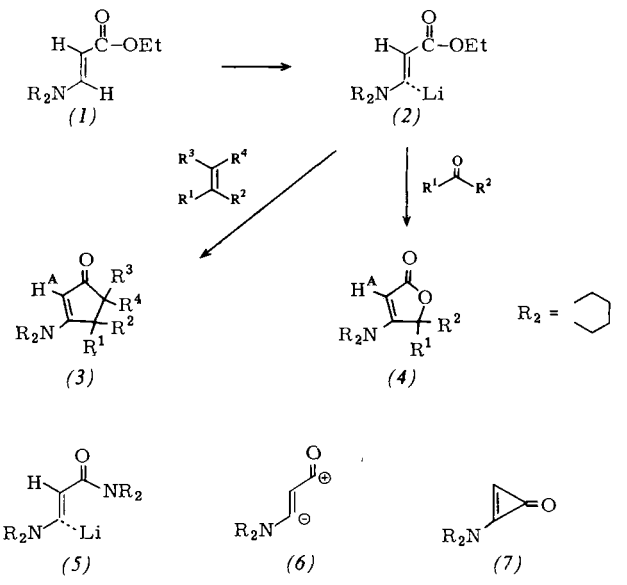
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[8] The compounds prepared were characterized by analysis and spectroscopy.

Facile Synthesis of Functionally Substituted Cyclopentenones and Butenolides from Functional Vinyl Carbanions[1]

By *Richard R. Schmidt* and *Jörg Talbiersky*[*]

Functional cyclopentenones and butenolides are of considerable importance as synthons in the chemistry of natural products. Numerous approaches to their synthesis have already been developed[2].

A new facile route starts from ethyl β-(1-pyrrolidinyl)acrylate *(1)*[3], which is transformed almost quantitatively into the β-alkoxycarbonylvinyllithium derivative *(2)* in a kinetically controlled reaction with *tert*-butyllithium below −100 °C. Surprisingly, under these conditions *(1)* hardly undergoes Michael addition and does not react at the ester group. Thus a functionalized C_3 synthon becomes accessible which has good nucleophilic and electrophilic properties. For this reason, ring closures with polar multiple bond systems which proved difficult or impossible with the vinyllithium derivative *(5)* described previously[4] should proceed readily. This is confirmed by the following reactions.



Reaction of *(2)* with α,β-unsaturated carbonyl compounds leads to functionalized 2-cyclopenten-1-ones *(3)* [cf. Table 1]. It should be noted in particular that Michael additions to the CC double bond of the β-aminoacrolein derivatives [products *(3c)* and *(3d)*] can be accomplished with the reagent. Equally surprising is the scope of the reaction of *(2)* with carbonyl compounds as hetero-multiple bond systems. Cyclizations to give the functionalized 2-buten-4-olides *(4)* are observed not only with aldehydes but also with normal esters [Table 1]. Thus the β-ethoxycarbonylvinyllithium derivative *(2)* proves to be a readily accessible equivalent of cyclopropenone, which is known to yield [3+2] cycloadducts by insertion of multiple bond systems—formally *via* the zwitterion *(6)*[5].

Table 1. Products of type *(3)* or *(4)* [a].

Cpd.	R^1	R^2	R^3	R^4	Yield [%] [b]	M. p. [°C] B. p. [°C/torr]	^{1}H-NMR (δ values, $CDCl_3$, TMS int.) H^A	H^B		H^C
(3a)	Ph	H^B	H^C	COtBu	67	156	5.10 (s)	4.17 (d)	or	3.95 (d) [d]
(3b)	COPh	H^B	H^C	COPh	25	191	4.97 (s)	5.52 (d)	or	4.52 (d) [d]
(3c)	$N(CH_2)_5$	H^B	H^C	COPh	49	105	4.92 (s)	4.72 (d)	or	4.60 (d) [d]
(3d)	$N(CH_2)_4$	H^B	H^C	COOEt	41	87	4.88 (s)	4.48 (d)		— [d, e]
(3e)	Ph	H^B	Ph	CN	32	219	4.83 (s)	5.43 (s)		—
(4a)	$OCH_2CH_3^B$	H^C	—	—	52	74	4.68 (s)	1.28 (t)		5.80 (s)
(4b)	OCH_3^B	$COOCH_3^C$	—	—	58	121	4.68 (s)	3.48 (s)		3.90 (s)
(4c)	OCH_3^B	$C_6H_5^C$	—	—	43	80	4.75 (s)	3.47 (s)		7.27–7.77 (m)
(4d)	H^B	$C_6H_5^C$	—	—	51	138, 180/10^{-2} [c]	4.68 (s)	5.72 (s)		7.40 (s)
(4e)	H^B	CH_3^C	—	—	49	90	4.42 (s)	4.92 (q)		1.50 (d)

[a] All compounds gave correct elemental analyses. [b] Yield of pure compound isolated. [c] Oven temperature on bulb tube distillation. [d] No assignment. [e] Cannot be determined from the spectrum.

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Experimental

Compound *(1)* (0.68 g, 4 mmol) is dissolved under N_2 in anhydrous tetrahydrofuran (50 ml). To this solution, cooled to −113 °C, is added dropwise a solution of *tert*-butyllithium in *n*-pentane (3 ml, 5.1 mmol; *ca.* 1.7 M solution). After 15 min the olefin or carbonyl compound (8 mmol) is added[6]. The solution is rapidly warmed to room temperature and stirred for a further 3 h[7]. After workup with water/chloroform, the dried (Na_2SO_4) $CHCl_3$ extract is evaporated down in a water-pump vacuum and the crude product is fractionated in a bulb tube [*(4a)*], recrystallized from ethyl acetate/light petroleum [*(4b)*], or chromatographed over silica gel. Eluent: ethyl acetate [*(3d)*, *(4e)*], benzene/acetone 7:3 [*(3c)*], ethyl acetate/light petroleum (low) 12:4 [*(4a)*], 10:2 [*(3e)*], ethyl acetate/methanol/light petroleum 7:1:14 [*(3a)*, *(3b)*].

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CAS Registry numbers:
(1), 65651-80-1; *(2)*, 65651-69-6; *(3a)*, 65651-70-9; *(3b)*, 65651-71-0; *(3c)*, 65651-72-1; *(3d)*, 65651-73-2; *(3e)*, 65651-74-3; *(4a)*, 65651-75-4; *(4b)*, 65651-76-5; *(4c)*, 65651-77-6; *(4d)*, 65651-78-7; *(4e)*, 65651-79-8
Olefinic precursor of *(3a)*, 29569-91-3; of *(3b)*, 959-28-4; of *(3c)*, 3506-37-4; of *(3e)*, 16610-80-3
Carbonyl precursor of *(4a)*, 109-94-4; of *(4b)*, 553-90-2; of *(4c)*, 93-58-3; of *(4d)*, 100-52-7; of *(4e)*, 75-07-0

[1] Vinyl Anions, Part 5. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 4: *R. R. Schmidt, J. Talbiersky*, Angew. Chem. *89*, 891 (1977); Angew. Chem. Int. Ed. Engl. *16*, 853 (1977).
[2] *G. A. Garcia, L. A. Maldonado, P. Crabbé* in *P. Crabbé*: Prostaglandin Research. Academic Press, New York 1977, p. 121; *Y. S. Rao*, Chem. Rev. *76*, 652 (1976).
[3] *Y. Postowskii, E. I. Grünblat, L. Trefilova*, Zh. Obshch. Khim. *31*, 400 (1961); Chem. Abstr. *55*, 23541 d (1961).
[4] *R. R. Schmidt, J. Talbiersky*, Angew. Chem. *88*, 193 (1976); Angew. Chem. Int. Ed. Engl. *15*, 171 (1976); Synthesis *1977*, 869.
[5] *R. Breslow, L. J. Altmann*, J. Am. Chem. Soc. *88*, 504 (1966), and references cited therein.
[6] 15 mmol of ester for synthesis of *(4a)*–*(4c)*.
[7] Stirring is continued for 18 h at room temperature in the case of *(3d)*.

Intramolecular Electron Transfer from Iron(II) to Cobalt(III) through 2,4,6-Pyridinetricarboxylate as Mediating Bridging Ligand[**]

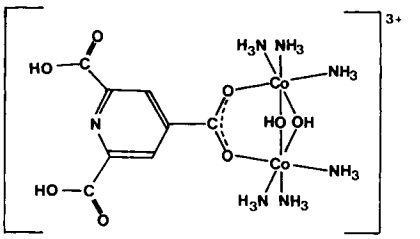
By *Horst Bertram* and *Karl Wieghardt*[*]

First order rate constants of electron transfer (ET) between two metal ions occurring within an encounter complex[1] or a true precursor complex[2] (inner-sphere reactions) have been determined by kinetic studies on redox reactions in only few cases. The activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of these intramolecular processes are considered to be important for further development of the theory of ET reactions[3].

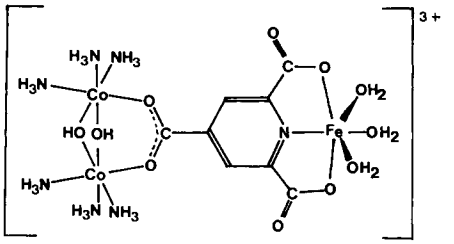
The red dinuclear Co^{III} complex *(1)* reacts with an excess of colorless $[Fe(OH_2)_6]^{2+}$ in O_2-free solutions of perchloric acid ($[H^+]=0.05$ to 1.0 mol/l) to form the violet 1:1 complex *(2)*:

$$(1)+[Fe(OH_2)_6]^{2+} \rightleftharpoons (2)+3H_2O+2H^+ \qquad (a)$$

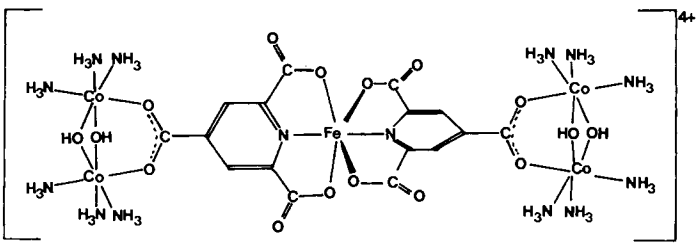
The absorption spectrum of *(2)* shows a maximum at $\lambda_{max}=525$ nm, $\varepsilon=900$ l/mol cm. Solutions of *(2)* can be stored for several hours at 25 °C without decomposition; *no* reduction of Co^{III} takes place with concomitant oxidation of Fe^{II}.



$[(Co^{III})_2]^{3+}$ *(1)*



$[(Co^{III})_2 Fe^{II}]^{3+}$ *(2)*



$[(Co^{III})_2 Fe^{II}(Co^{III})_2]^{4+}$ *(3)*

At higher pH values (4 to 7) and with an excess of *(1)*, however, an intensely violet 2:1 complex is formed which probably has the structure *(3)* ($\lambda_{max}=557$ nm, $\varepsilon=2350$ l/mol cm):

$$(2)+(1) \overset{K}{\rightleftharpoons} (3)+3H_2O+2H^+ \qquad (b)$$

Complex *(3)* decomposes by a first-order process to form one Co^{II} and one Fe^{III} ion per complexed cation *(3)*:

$$[(Co^{III})_2Fe^{II}(Co^{III})_2]^{4+} \xrightarrow{k_{et}} [Co^{II}Co^{III}Fe^{III}(Co^{III})_2]^{4+} \qquad (c)$$

The kinetics of the reaction was measured using pseudo-first order conditions with an excess of *(1)* in a phthalic acid buffer (pH 5.5, ionic strength 0.04 mol/l) (Fig. 1). The dependence of the rate constant k_{obs} [s^{-1}] upon the complex concentration $[(Co^{III})_2]$ at constant $[H^+]$ can be described by equation (d), derived formally for a mechanism according to eq. (b) and (c):

$$k_{obs}=\frac{k_{et}K[(Co^{III})_2]}{1+K[(Co^{III})_2]} \qquad (d)$$

When $K\cdot[(Co^{III})_2] \gg 1$, the reaction rate is independent of $[(Co^{III})_2]$ and $k_{obs}=k_{et}$.

Figure 1 shows that this condition is fulfilled for $[(Co^{III})_2] \geq 5\times10^{-4}$ mol/l and pH = 5.5 in the temperature range investigated. The intramolecular ET rate constant k_{et}

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

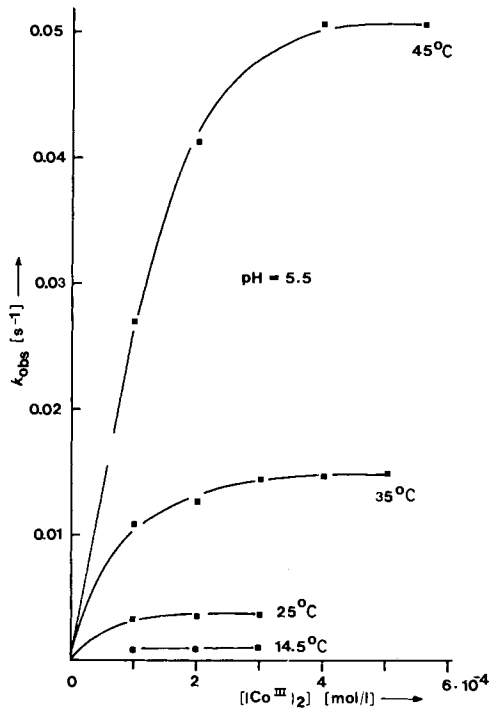


Fig. 1. Dependence of the rate constant k_{obs} on the concentration of complex *(1)* ($[Fe(OH_2)_6^{2+}] = 0.2 \times 10^{-4}$ mol/l, pH = 5.5 (phthalic acid buffer), ionic strength = 0.04 mol/l).

was determined at 14.5 (0.8×10^{-3}), 25 (3.7×10^{-3}), 35 (14.6×10^{-3}), and 45 °C ($50.7 \times 10^{-3}\,s^{-1}$). The activation parameters are calculated as $\Delta H^{\neq} = 24.0 \pm 0.2$ kcal/mol, $\Delta S^{\neq} = 11 \pm 1$ cal/mol K.

The proposed mechanism is substantiated by the following experiment: the change in absorption ($\lambda = 540$ nm) of a solution of *(1)* and $[Fe(OH_2)_6]^{2+}$ in the ratio of 2:1 plotted as a function of pH shows (Fig. 2) that formation of complex *(3)* is complete at pH > 4.5. A plot of the rate constant k_{obs} *versus* the pH value of the same solution follows as parallel course: a limiting value ($3.9 \times 10^{-3}\,s^{-1}$) is reached at pH 4.5 which corresponds to the value of k_{et} for decomposition of *(3)*; at low pH values k_{obs} becomes zero.

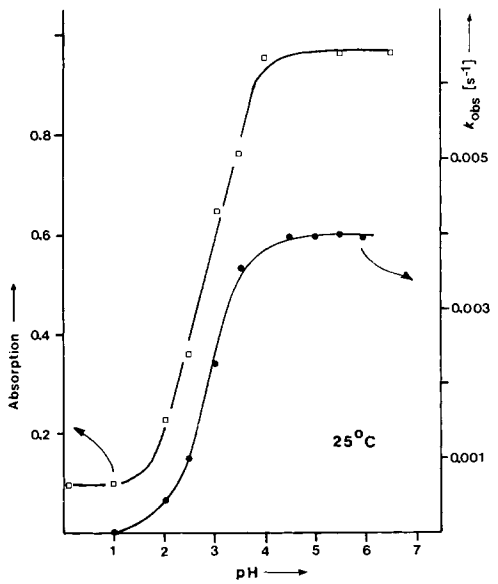


Fig. 2. a) Dependence of the absorption at $\lambda = 540$ nm of a solution of *(1)* (2×10^{-4} mol/l) and $[Fe(OH_2)_6]^{2+}$ (1×10^{-4} mol/l) on the pH value at 25 °C (□); b) dependence of the rate constant of decomposition of *(3)*, k_{obs}[s^{-1}], in the same solution, on the pH value at 25 °C (●).

In structures *(2)* and *(3)* the redox-active metal ions Fe^{II} and Co^{III} are separated by about 860 pm by the organic ligands; there is no experimental evidence for direct interaction between the two centers. Now *(2)* is redox-inactive whereas *(3)* undergoes intramolecular electron transfer yielding Co^{II} and Fe^{III} (an intermolecular decomposition of *(3)* by an outer-sphere process is not consistent with the observed kinetics). The reducing action of Fe^{II} in the coordination of *(2)* is apparently insufficient to put an electron into the LUMO of the organic ligand. This mechanism only becomes possible on further coordination of *(2)* with *(1)* ("chemical" or radical ion mechanism[3]).

Thus electron transfer proceeds through the organic ligand, which may be reduced, thereby generating a transient radical cation[4, 5]:

$$(3) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [(Co^{III})_2\text{—}\dot{L}^{-}\text{—}Fe^{III}(Co^{III})_2]^{4+} \xrightarrow{k_2} \text{Products} \qquad \text{(e)}$$

($\dot{L}$ = reduced pyridinetricarboxylate ligand)

The observed rate constant k_{et} can represent two limiting cases if the reaction proceeds according to (e): if k_{-1} is much greater than k_2, the $k_{et} = K_1 \cdot k_2$ ($K_1 = k_1/k_{-1}$). In contrast, if k_2 is greater than k_{-1}, then $k_{et} = k_1$, *i.e.* formation of the radical cation is rate determining. No decision is yet possible as to which of the two alternatives is actually encountered.

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CAS Registry numbers:
(1), 65651-26-5; *(2)*, 65701-64-6; *(3)*, 65651-33-4; $[Fe(OH_2)_6]^{2+}$, 15365-81-8

[1] *D. Gaswick, A. Haim*, J. Am. Chem. Soc. *93*, 7347 (1971); *L. A. A. Oliveira, H. E. Toma, E. Giesbrecht*, Inorg. Chim. Acta *22*, 269 (1977).
[2] *R. D. Cannon, J. Gardiner*, Inorg. Chem. *13*, 390 (1974); *S. S. Isied, H. Taube*, J. Am. Chem. Soc. *95*, 8198 (1973); *H. Fischer, G. M. Tom, H. Taube, ibid. 98*, 5512 (1976); *J. Iwo, A. Haim, ibid. 98*, 1172 (1976).
[3] *A. Haim*, Acc. Chem. Res. *8*, 264 (1975).
[4] A radical cation of this type could be detected directly in another system: *H. Spiecker, K. Wieghardt*, Inorg. Chem. *16*, 1290 (1977).
[5] A complex with electronically excited $(Co^{II})^*$ has recently been proposed as an alternative intermediate: *K. Rieder, H. Taube*, J. Am. Chem. Soc. *99*, 7891 (1977).

Regiospecific and Enantioselective Aldol Reactions[**]

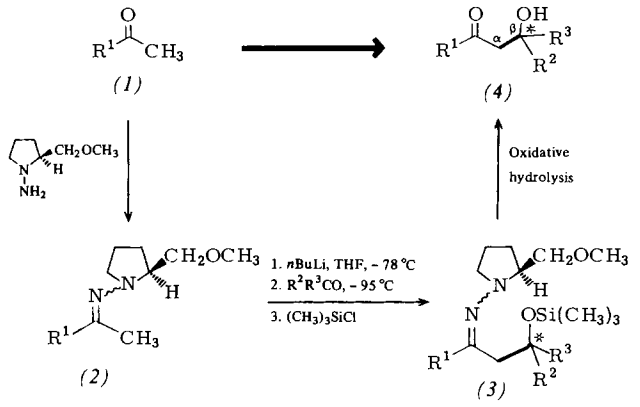
By *Herbert Eichenauer, Edgar Friedrich, Werner Lutz*, and *Dieter Enders*[*]

The aldol reaction[1] is one of the basic methods for CC linkage and its intramolecular version one of the principal techniques for preparing five- and six-membered rings. The synthetic utility of intermolecular aldol reactions has hitherto been limited by side reactions. While directed[2] and regiospecific[3] aldol reactions have meanwhile been developed, there are still no generally applicable diastereo-[4] and enantioselective procedures available[5].

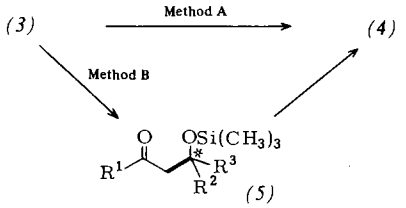
We now report the first regiospecific and enantioselective aldol reactions *(1)* → *(4)*. The ketones *(1)* are first transformed into the chiral hydrazones *(2)*[6], metalated with *n*-butyllith-

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and by a Liebig Fellowship awarded to *D. E.* by the Verband der Chemischen Industrie. Presented in part at Chemical Colloquia held at Frankfurt, Marburg, and München, November/December 1977.

ium in tetrahydrofuran, treated at −95 °C with carbonyl compounds, and the resulting adducts silylated by chlorotrimethylsilane to form the doubly protected ketols *(3)*. Oxidative hydrolysis finally affords the chiral ketols *(4)* in good chemical yields and enantiomeric excesses of 31–62%.



Two approaches were used for the step *(3)*→*(4)*: reaction with 30% hydrogen peroxide at pH 7 in methanol leads directly to the ketols *(4)* (method A); alternatively, the silylated ketols *(5)* are initially produced by sensitized photooxidation[7] in tetrahydrofuran and reductive hydrolysis; compounds *(5)* can readily be cleaved to give *(4)* (method B). The results are summarized in Table 1[8].



The absolute configuration of the optically active ketols *(4)* is not yet known; the enantiomeric excesses were determined by NMR spectroscopy. The new asymmetric C—C linkages occur regiospecifically at the less substituted α-carbon atom of the ketones *(1)* (chiral center at β-C).

General procedure

The new hydrazones *(2)* are produced by known methods[6]. A 1.6 M solution (6.2 ml) of *n*-butyllithium in *n*-hexane is added to a stirred solution of *(2)* (10 mmol) in tetrahydrofuran (25 ml) at −78 °C. The reaction mixture is warmed to 0 °C over 1 h and then cooled to −95 °C. Aldehyde or ketone (10 mmol) is then added dropwise and the temperature allowed to rise to −20 °C over 12 h. Chlorotrimethylsilane (10.5 mmol) is added at −60 °C, and the mixture stirred for 1 h at room temperature. Workup with CH_2Cl_2, drying over sodium sulfate, and removal of solvent gives *(3)* as a viscous oil.

Cleavage by method A: (3) is dissolved in methanol (20 ml) and stirred with buffer (pH 7, 10 ml) and 30% hydrogen peroxide (10 ml) for 2–24 h at 20–80 °C (TLC check). Workup with ether, drying over magnesium sulfate, and removal of solvent gives the ketols *(4)* which are purified by distillation.

Cleavage by method B: (3) is dissolved in tetrahydrofuran and cleaved as already described[7] by sensitized photooxidation at −78 °C (irradiation time 4.5–10.5 h) followed by reduction with dimethyl sulfide and hydrolysis. Workup with CH_2Cl_2, drying over sodium sulfate, removal of solvent, and distillation furnishes the ketols *(5)*. Solvolysis in methanol (5 ml) containing a catalytic amount of HCl (5–10 min, 20 °C), neutralization with sodium hydrogen carbonate and workup with CH_2Cl_2 gives the ketols *(4)*, which are purified by distillation or recrystallization.

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(1a), 67-64-1; *(1d)*, 78-93-3; *(1e)*, 563-80-4; *(1f)*, 75-97-8; *(2a)*, 65651-52-7; *(2d)*, 65651-53-8; *(2e)*, 65651-54-9; *(2f)*, 65651-55-0; *(3a)*, 65651-56-1; *(3b)*, 65651-57-2; *(3c)*, 65651-58-3; *(3d)*, 65651-59-4; *(3e)*, 65651-60-7; *(3f)*, 65651-61-8; *(4a)*, 65651-62-9; *(4b)*, 65651-63-0; *(4c)*, 65651-64-1; *(4d)*, 65651-65-2; *(4e)*, 65651-66-3; *(4f)*, 65651-67-4; *(5a)*, 65651-68-5; *(5e)*, 65651-50-5; *(5f)*, 65651-51-6; (*S*)2-(methoxymethyl)-1-pyrrolidinamine, 59983-39-0

[1] Review: *H. Stetter* in Houben/Weyl/Müller: Methoden der organischen Chemie, Vol. VII/2b. Thieme, Stuttgart 1976, p. 1449.
[2] *G. Wittig*, Fortschr. Chem. Forsch. *67*, 1 (1976).
[3] *E. J. Corey, D. Enders*, Chem. Ber., in press, and references cited therein; *T. Inoue, T. Uchimaru, T. Mukaiyama*, Chem. Lett. *1977*, 153; *R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, M. Shimizu*, J. Am. Chem. Soc. *99*, 1265 (1977).
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Table 1. Chiral β-ketols *(4)* prepared by enantioselective carbonyl addition. H_2O_2 (A) or $^1O_2$ (B) was used for oxidative cleavage of the hydrazones *(3)*.

	R¹	R²	R³	B.p. [°C/torr] [a] M.p. [°C]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$) [b]	E. e. [%] [c] A	E. e. [%] [c] B	Yield [%] [d] A	Yield [%] [d] B [e]
(4a)	Me	H	*n* Bu	110/0.3	−15.8° (0.6)	27	36	77	48
(4b)	Me	H	*i* Pr	50/0.15 (83–84/12) [f]	−18.5° (1.0)	40		72	
(4c)	Me	Me	*i* Pr	80/0.4 (35/0.1) [g]	+ 1.95 ° (0.85)	47		58	
(4d)	Et	Me	*t* Bu	70/0.9 (71/2) [h]	− 2.35° (0.8)	39		57	
(4e)	*i* Pr	H	*t* Bu	105/0.2	+28.0° (4.45)	31	17	42 [i]	51
(4f)	*t* Bu	H	Cyclo-hexyl	63–64 (B) 48 (A)	−14.9° (1.85) [j]	<10	62	60	32

[a] Oil-bath temperature on molecular distillation. [b] Highest rotation of ketols *(4)* prepared by route A and purified by preparative gas chromatography. [c] Determined by NMR spectroscopy with the shift reagent tris[3-(heptafluoro-1-hydroxybutylidene)-D-camphorato]europium(III) (Aldrich Co.). [d] Yield of distilled ketols *(4)* shown to be >90% pure by gas chromatography, based on ketone *(1)*. [e] Yield of silylated ketol *(5)*. [f] *R. Heilmann, G. de Gaudemaris, P. Arnaud, G. Scheuerbrandt*, Bull. Soc. Chim. Fr. *1975*, 112. [g] *J. Michel, P. Canonne*, Can. J. Chem. *49*, 4084 (1971). [h] *V. I. Esafov, A. A. Vshivkov, L. V. Markova, L. I. Svalova*, Zh. Org. Khim. *1973*, 235; Chem. Abstr. *79*, 18297t (1973). [i] 20% of the condensation product 2,6,6-trimethyl-4-hepten-3-one were also isolated. [j] Rotation of the crude product (B): $[\alpha]_D^{20} = -15.7°$ (7.95, $CHCl_3$); these values are presumably reduced by traces of a strongly (+)-rotatory contaminant. Repeated crystallization gave practically enantiomerically pure *(4f)*, m.p. 63 °C, $[\alpha]_D^{20} = -47.5°$ (0.8, $CHCl_3$).

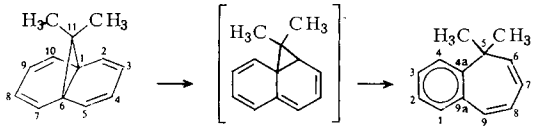
[5] Intramolecular asymmetric aldol reactions: *A. Fischli*, Chimia *30*, 4 (1976); *N. Cohen*, Acc. Chem. Res. *9*, 412 (1976); aldol-type asymmetric reactions; *J. D. Morrison, H. S. Mosher*: Asymmetric Organic Reactions. Prentice-Hall, Englewood Cliffs 1971; *C. Mioskowski, G. Solladié*, J. Chem. Soc. Chem. Commun. *1977*, 162; *I. Ojima, K. Yoshida, S. Inaba*, Chem. Lett. *1977*, 429.
[6] *D. Enders, H. Eichenauer*, Angew. Chem. *88*, 579 (1976); Angew. Chem. Int. Ed. Engl. *15*, 549 (1976); Tetrahedron Lett. *1977*, 191.
[7] For the cleavage of dimethylhydrazones with singlet oxygen, see *E. Friedrich, W. Lutz, H. Eichenauer, D. Enders*, Synthesis *1977*, 893.
[8] All new compounds gave correct elemental analyses. IR, NMR, and mass spectra are in agreement with the structures given.

The Berson-Willcott Rearrangement of 11,11-Dimethyltricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene and Its Radical Anion[**]

By *Fabian Gerson, Walter Huber*, and *Klaus Müllen*[*]

The nature of the frontier orbitals of a molecule is of prime importance for the discussion of its valence isomerizations[1]. It is therefore of interest to investigate the way in which the formation of the corresponding radical anion affects such a conversion. While mechanistic studies of this kind have thus far been mainly restricted to pericyclic reactions of the $n\pi+\sigma\rightarrow(n+1)\pi$ type[2], the present work on 11,11-dimethyltricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene *(1)*[3] permits the first comparison between the *Berson-Willcott*[4] rearrangement of a norcaradiene derivative and the analogous valence isomerization of its radical anion.

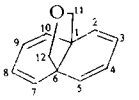
As has been observed by *Vogel et al.*[5], thermolysis of *(1)* leads to 5,5-dimethylbenzocycloheptene *(3)*. This reaction, which proceeds *via* the transient valence isomer *(2)*, mimics the rearrangement described by *Berson* and *Willcott* for the parent cycloheptatriene-norcaradiene system.



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

We investigated the kinetics of the thermolysis of *(1)* by monitoring the intensities of the ^{1}H-NMR signals of *(1)* and *(3)* in the range of 150 to 190 °C. The resulting activation parameters are listed in Table 1[6].

Reduction of *(1)* with potassium in 2-methyltetrahydrofuran below −110 °C enabled us to record the ESR spectrum of the primary radical anion *(1)*$^{\bullet\ominus}$[7]. The similarity between the hyperfine data of *(1)*$^{\bullet\ominus}$ (Table 2) and those of the radical anion of the reference compound *(4)*[8] indicates that *(1)*$^{\bullet\ominus}$, like *(4)*$^{\bullet\ominus}$, contains two separate butadiene π-systems[9].



(4)

Upon warming of the solution of *(1)*$^{\bullet\ominus}$ above −110 °C, the spectrum of the primary radical anion was gradually replaced by that of a secondary paramagnetic species. This spectrum, which also appears on direct reduction of *(3)*, has been analyzed by the ENDOR technique[7]; its hyperfine data (Table 2) are fully consistent with the structure of the radical anion *(3)*$^{\bullet\ominus}$[10].

Table 1. Activation parameters for the valence isomerizations *(1)*→*(3)* and *(1)*$^{\bullet\ominus}$→*(3)*$^{\bullet\ominus}$.

	k (25 °C) [s^{-1}]	log A	E_a [kJ/mol]	$\Delta H^{\neq}$ (25 °C) [kJ/mol]	$\Delta S^{\neq}$ (25 °C) [J/mol·K]
(1)→*(3)*	≈10^{-12}	13.4±0.3	150±2	147±2	4±4
(1)$^{\bullet\ominus}$→*(3)*$^{\bullet\ominus}$	≈10^3	13±2 [a]	46±8 [a]	43±8 [a]	20±20 [a]

[a] Large range of error is due to the very rapid course of the reaction.

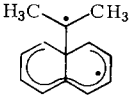
Table 2. ^{1}H- and ^{39}K coupling constants [G], a_{H_μ} and a_K, respectively, for the radical anions *(1)*$^{\bullet\ominus}$, *(4)*$^{\bullet\ominus}$, and *(3)*$^{\bullet\ominus}$.

	a_{H_μ}									a_K
	μ = 2, 5, 7, 10				3, 4, 8, 9				11 (12)	
(1)$^{\bullet\ominus}$	4.16				1.75				0.25 [a]	0.22
(4)$^{\bullet\ominus}$	3.80				1.51				0.45 [b]	0.20
μ =	6	7	8	9	4	3	2	1	5	
(3)$^{\bullet\ominus}$	7.34	2.68	4.93	4.55	0.21	4.05	1.40	3.16	0.86 [a]	0.17

[a] Six methyl protons. [b] Four methylene protons.

Starting from *(1)*, the ESR signals of both radical anions were readily observed in the range of −100 to −70 °C and thus the kinetics of the valence isomerization *(1)*$^{\bullet\ominus}$→*(3)*$^{\bullet\ominus}$ could be deduced from the changes in the signal intensities. The pertinent activation parameters (Table 1) differ strikingly from corresponding values for the rearrangement *(1)*→*(3)*. In the case of the radical anion, the rate constant k (25 °C) is higher by a factor of 10^{15}, and the activation enthalpy $\Delta H^{\neq}$ (25 °C) lower by *ca.* 100 kJ/mol, than for the neutral compound.

It has been concluded from the stereospecificity of the thermolysis of structurally related compounds of lower symmetry that the isomerization *(1)*→*(3)* proceeds concertedly[11]. On the other hand, the considerable enhancement of the rate constant for the radical anion can be easily rationalized if one assumes the biradical *(5)*•• and its reduced form *(5)*$^{\bullet\ominus}$ to be intermediates in *(1)*→*(3)* and *(1)*$^{\bullet\ominus}$→*(3)*$^{\bullet\ominus}$, respectively[12].



(5)••

Beyond the mechanistic aspects, such an enhancement has potential preparative applications. Reduction and subsequent reoxidation would yield a valence isomer of the neutral compound under relatively mild conditions.

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CAS Registry numbers:
(1), 38963-97-2; *(1)*, radical anion, 65636-00-2; *(3)*, 65635-99-6; *(3)*, radical anion, 65701-69-1; *(4)*, radical anion, 65701-70-4

[1] See, *e.g.*, *R. B. Woodward, R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. Int. Ed. Engl. *8*, 781 (1969).
[2] *S. F. Nelsen, J. P. Gillespie*, J. Org. Chem. *38*, 3592 (1973); J. Am. Chem. Soc. *95*, 2940 (1973); *N. L. Bauld, J. Cessac, C. S. Chang, F. R. Farr, R. Holloway, ibid. 98*, 4561 (1976).
[3] *E. Vogel*, Pure Appl. Chem. *20*, 237 (1969). *E. de Cleur*, Ph. D. thesis, Universität Köln 1969.
[4] *J. A. Berson, M. R. Willcott III*, J. Am. Chem. Soc. *87*, 2752 (1965); *88*, 2494 (1966).
[5] a) *E. Vogel*, personal communication; b) *G. Jabs*, Ph. D. thesis, Universität Köln 1971.
[6] These parameters agree within the limits of error with the corresponding values in ref. [5b].
[7] Experimental details, in particular those concerning the ESR and ENDOR spectra, will be published in a forthcoming paper.
[8] *F. Gerson, E. Heilbronner, W. A. Böll, E. Vogel*, Helv. Chim. Acta *48*, 1494 (1965).
[9] This finding also permits unequivocal assignment of the coupling constants to the two sets of four equivalent ring protons in $(1)^{\cdot\ominus}$.
[10] The assignment of the coupling constants to the eight single ring protons in $(3)^{\cdot\ominus}$ is largely based on correlation with π-spin populations calculated according to the *McLachlan* procedure [*A. D. McLachlan*, Mol. Phys. *3*, 233 (1960)].
[11] *F. G. Klärner*, unpublished work, quoted in ref. [5b].
[12] In contrast to $(1)^{\cdot\ominus}$ where the additional electron occupies the lowest *antibonding* orbital of one butadiene π-moiety, in $(5)^{\cdot\ominus}$ such an electron enters the *nonbonding* orbital of the nonatetraenyl π-system. The difference in π-energies (0.62β in the HMO model) would facilitate the opening of the three-membered ring in the radical anion $[(1)^{\cdot\ominus} \rightarrow (5)^{\cdot\ominus}]$ relative to the neutral compound $[(1) \rightarrow (5)^{\cdot\cdot}]$ and thus lower the activation energy.

Regioselective Synthesis of Isomeric Bicyclic Peroxides[**]

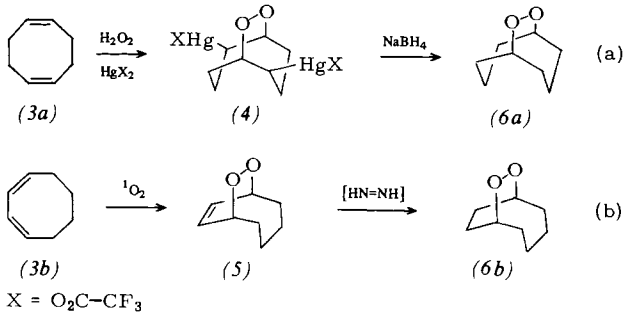
By *Waldemar Adam, A. John Bloodworth, Henny J. Eggelte*, and *Mark E. Loveitt*[*]

Monocyclic peroxides *(1)* have recently been shown to serve as useful synthons for the preparation of unusual organic molecules[1]. Equally importantly they constitute valuable precursors of the mechanistically interesting diradicals[2]. The geometrical contraint in bicyclic peroxides *(2)* is expected to impart new synthetic and mechanistic behavior, but unfortunately no general and convenient methods are presently available for the preparation of such compounds.

(1)   *(2)*

In this communication we describe potentially general routes to isomeric bicyclic peroxides involving: a) reaction of non-conjugated cyclic dienes with hydrogen peroxide and mercury bis(trifluoroacetate) (peroxymercuration) followed by reduction with $NaBH_4$[3], and b) photooxygenation of conjugated cyclic dienes followed by reduction with azodicarboxylate[4].

These complementary and regioselective peroxybicyclizations are illustrated for the saturated compounds 9,10-dioxabicyclo[3.3.2]decane (1,5-epidioxycyclooctane) *(6a)* and 7,8-dioxabicyclo[4.2.2]decane (1,4-epidioxycyclooctane) *(6b)*, respectively.



When the diene *(3a)* was added to a mixture of hydrogen peroxide (85—95 %) and mercuric trifluoroacetate in CH_2Cl_2 at room temperature, equal amounts of the bicyclic peroxide *(4)* and the corresponding bicyclic ether were formed [use of $Hg(NO_3)_2 \cdot H_2O$[3] in this particular case affords only the ether]. The products were separated by dissolving the mixture in benzene, whereupon crystals of the pure (solvated) peroxide were precipitated[5]. Reduction of *(4)* in CH_2Cl_2 with $NaBH_4$ in aqueous NaOH gave the previously unknown cyclic peroxide *(6a)*[6], together with an approximately equal amount of 4-cycloocten-1-ol. Catalytic hydrogenation of *(6a)* over Pd/C led quantitatively to the known *cis*-1,5-cyclooctanediol[7], m.p. 73–75 °C.

On the other hand, photooxygenation of the diene *(3b)* in CH_2Cl_2 with tetraphenylporphyrin as sensitizer gave the known[8] unsaturated peroxide *(5)*, which on reduction with azodicarboxylate[4] in methanol afforded the previously unknown saturated peroxide *(6b)*[9]. Catalytic hydrogenation of *(6b)* over Pd/C gave quantitatively the known *cis*-1,4-cyclooctanediol[10], m.p. 81—83 °C.

For the first time saturated bicyclic peroxides with medium-sized rings have become conveniently available from readily accessible starting materials. Furthermore, *(6a)* is the first bicyclic peroxide to be prepared that does not contain a 1,2-dioxane ring.

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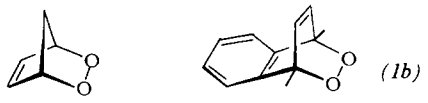
[1] *W. Adam*, Angew. Chem. *86*, 683 (1974); Angew. Chem. Int. Ed. Engl. *13*, 619 (1974).
[2] *W. Adam, J. Sanabia*, Angew. Chem. *85*, 914 (1973); Angew. Chem. Int. Ed. Engl. *12*, 843 (1973); *L. Salem, C. Rowland, ibid. 84*, 86 (1972) and *11*, 92 (1972), respectively.
[3] *A. J. Bloodworth, M. E. Loveitt*, J. Chem. Soc. Chem. Commun. *1976*, 94; J. Chem. Soc. Perkin I *1978*, in press.
[4] *W. Adam, H. J. Eggelte*, Angew. Chem. *89*, 762 (1977); Angew. Chem. Int. Ed. Engl. *16*, 713 (1977).
[5] Solvated *(4)* was isolated in 42 % yield, m.p. 118—119 °C (dec.); elemental analysis indicated the presence of 0.81 equivalents of benzene. ^{13}C-NMR ($CDCl_3$, TMS): δ = 128.6 (C_6H_6), 85.3, 48.4, 34.1, 29.1.
[6] *(6a)* was isolated in 25 % yield by chromatography on SiO_2/CH_2Cl_2, and purification by fractional sublimation (45 °C/15 torr); m.p. 116—118 °C; ^1H-NMR (CCl_4, TMS): δ = 1.50—2.30 (m, 12H) 4.35—4.65 (m, 2H); ^{13}C-NMR ($CDCl_3$, TMS): δ = 83.96, 31.38, 23.82; MS: m/e = 142 (7 %), 55 (100).

[7] M.p. 73.8—74.8 °C: *A. C. Cope, A. H. Keough, P. E. Peterson, H. E. Simmons, G. W. Wood*, J. Am. Chem. Soc. *79*, 3900 (1957).
[8] *Y. Kayama, M. Oda, Y. Kitahara*, Chem. Lett. *1974*, 345.
[9] *(6b)* was isolated in 20% yield by chromatography on $SiO_2/CHCl_3$, and purification by fractional sublimation (45 °C/10 torr); m.p. 96—98 °C; ^{1}H-NMR (CCl_4, TMS): $\delta = 1.25$—2.45 (m, 12H), 4.20—4.60 (m, 2H); ^{13}C-NMR ($CDCl_3$, TMS): $\delta = 76.02$, 34.60, 24.46, 20.68; MS: $m/e = 142$ (9%), 55 (100); the multiplet of the 12 methylene protons is less symmetrical than in *(6a)*.
[10] M.p. 83.2—84 °C; *A. C. Cope, J. M. Grisar, P. E. Peterson*, J. Am. Chem. Soc. *81*, 1640 (1959).

Trapping of Unstable Fulvene/Singlet Oxygen Adducts by Reduction with Diazene[**]

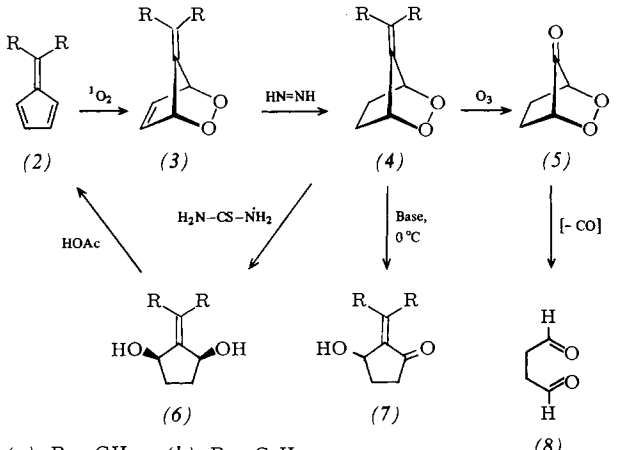
By *Waldemar Adam* and *Ihsan Erden*[*]

We recently reported that diimide (diazene) selectively reduces the double bond in the unstable endoperoxides *(1a)* and *(1b)*, derived respectively from singlet oxygenation of cyclo-



pentadiene[1] and 1,4-dimethylnaphthalene[1b], without severing the labile peroxide linkage. This novel, selective reduction should constitute a convenient and effective chemical tool for the characterization of unstable endoperoxides derived from singlet oxygenations since the basic peroxide skeleton is preserved. Furthermore, it offers a unique entry into unusual and hitherto inaccessible cyclic peroxides. We demonstrate the feasibility and potential of this methodology with the unstable peroxides *(3a)* and *(3b)*, formed from 6,6-dimethyl- and 6,6-diphenylfulvene, respectively.

Singlet oxygenation of 6,6-disubstituted fulvenes *(2)* leads to a complex mixture of products, postulated to be derived from the labile epidioxyfulvene *(3)* by rearrangement[2]. NMR evidence for the intervention of *(3)* could be secured when the singlet oxygenation was carried out at −70 °C; but above −20 °C the unstable *(3)* afforded the previously observed complex product mixture[3].



On treatment of a CH_2Cl_2 solution of *(3a)*, prepared from 6,6-dimethylfulvene *(2a)* by photo-oxygenation at −78 °C with tetraphenylporphyrin as sensitizer and a General Electric 400W sodium lamp, with diimide which was generated *in situ* at −78 °C as described previously[1a], the stable cyclic peroxide *(4a)* was isolated in 63% overall yield as white needles (m.p. 53 °C) after recrystallization from CH_2Cl_2/CH_3OH (1:3). Structural proof for *(4a)* rests on satisfactory elemental analysis, spectral data[4] and chemical transformations. Thus, reduction with thiourea in CH_3OH at 0 °C gave the diol *(5a)*[5], which could be dehydrated back to the fulvene *(2a)* on refluxing in acetic acid for one hour. On treatment with triethylamine in CH_2Cl_2 at 0 °C, *(4a)* is converted into *(7a)*[6].

Similarly, *(2b)* gave the cyclic peroxide *(4b)* in 88% overall yield on photo-oxygenation and diimide reduction at −78 °C, m.p. 77–78 °C (from 2:1 C_6H_6/CH_3OH)[7]. The reactions of the phenyl derivatives *(4b)*→*(6b)*[8] and *(6b)*→*(2b)* could be accomplished under the same conditions as used for the methyl derivatives. *(4b)* can be converted into *(7b)* by treatment with methanolic KOH at 0 °C[9].

Ozonolysis of *(3a)* and *(3b)* in CH_2Cl_2 at −78 °C in the presence of tetracyanoethylene produced an unstable substance which exhibited proton resonances at $\delta = 2.0$ (m, 4H) and 4.38 (m, 2H), besides acetone and benzophenone. When the ozonolyzate was allowed to warm up to −10 °C, the substance decarbonylated cleanly into succinaldehyde *(8)*. On the basis of these facts we assign the compound the novel epidioxyketone structure *(5)*. Interestingly, *(5)* decarbonylates with emission of light; it can therefore be regarded as a "energy reservoir".

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CAS Registry numbers:
(2a), 2175-91-9; *(2b)*, 2175-90-8; *(3a)*, 51027-90-8; *(3b)*, 65651-42-5; *(4a)*, 65651-43-6; *(4b)*, 65651-44-7; *(5)*, 65651-45-8; *(6a)*, 65651-46-9; *(6b)*, 65651-47-0; *(7a)*, 65651-48-1; *(7b)*, 65651-49-2; *(8)*, 638-37-9; diazene, 3618-05-1

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[**] Cyclic Peroxides, Part 64. This work was supported by the Petroleum Research Fund (Grant 8341-AC-1,4), administered by the American Chemical Society, the National Science Foundation (Grant CHE-72-04956-A-04) and the National Institutes of Health (Grants GM-22119-02, GM-00141-02, and RR-8102-04).—Part 63: *W. Adam, A. J. Bloodworth, H. J. Eggelte, M. E. Loveitt*, Angew. Chem. *90*, 216 (1978); Angew. Chem. Int. Ed. Engl. *17*, 209 (1978).

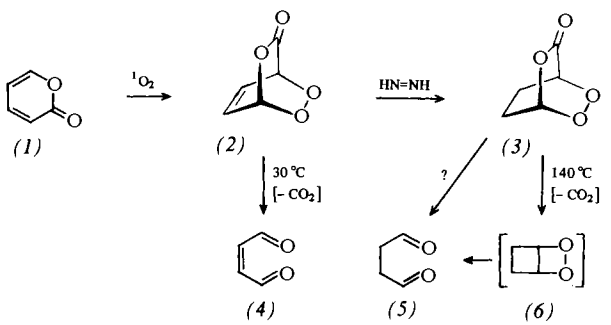
[1] a) *W. Adam, H. J. Eggelte*, J. Org. Chem. *42*, 3978 (1977); b) Angew. Chem. *89*, 762 (1977); Angew. Chem. Int. Ed. Engl. *16*, 713 (1977).
[2] *W. Skorianetz, K. H. Schulte-Elte, G. Ohloff*, Angew. Chem. *84*, 311 (1972); Angew. Chem. Int. Ed. Engl. *11*, 330 (1972); *N. Harada, S. Suzuki, H. Uda, H. Ueno*, J. Am. Chem. Soc. *94*, 1777 (1972).
[3] *N. Harada, H. Uda, H. Ueno, S.-I. Utsumi*, Chem. Lett. *1973*, 1173; *N. Harada, S. Kudo, H. Uda, S. Utsumi, ibid. 1974*, 893.
[4] *(4a)*, ^{1}H-NMR (CCl_4, TMS): $\delta = 1.80$ (s, 6H), 1.50–2.15 (m, 4H), 4.58 (m, 2H); IR (CCl_4): 2990, 2960, 2875, 1470, 1360, 1270, 1180 m^{-1}; MS: $m/e = 140$.
[5] *(6a)*, b. p. 93–95 °C (from CH_3OH/Ether (1:1)), yield 84%; ^{1}H-NMR ($CDCl_3$, TMS): $\delta = 1.90$ (s, 6H), 1.75–2.00 (m, 4H), 2.35 (br. m, 2OH), 4.75 (m, 2 O—C—H).
[6] *(7a)*, b. p. 78 °C/0.4 torr; $n_D^{20} = 1.5050$; yield 76%; ^{1}H-NMR ($CDCl_3$, TMS): $\delta = 1.70$–2.70 (m, 4H), 2.05 and 2.30 (s, 6H), 2.60 (m, OH), 4.94 (m, O—C—H).
[7] *(4b)*, ^{1}H-NMR (CCl_4, TMS): $\delta = 1.95$ (m, 4H), 4.65 (m, 2H), 7.10 (br. s, 10H); IR (CCl_4): 3100, 2980, 1470, 1435, 1210, 1025, 900 cm^{-1}; MS: $m/e = 264$.
[8] *(6b)*, m. p. 148–149 °C (needles from CH_3OH/H_2O); yield 88%; ^{1}H-NMR (CD_3OD, TMS): $\delta = 1.60$ (m, 4H), 4.30 (m, 2 O—C—H), 4.48 (s, 2OH), 6.97 (br. s, 10H).
[9] *(7b)*, m.p. 163–164 °C (dec.) (from CH_3OH/H_2O (3:1)); yield 66%; ^{1}H-NMR ($CDCl_3$, TMS): $\delta = 1.78$–2.85 (m, 4H), 1.96 (m, OH), 4.82 (m, O—C—H), 7.20 (m, 10H).

Trapping of Unstable α-Pyrone/Singlet Oxygen Adduct by Reduction with Diazene[**]

By *Waldemar Adam* and *Ihsan Erden*[*]

Unstable endoperoxides such as the singlet oxygen adducts of cyclopentadiene[1a], fulvenes[1b], and furans[1c] can be conveniently and selectively reduced to their respective dihydroendoperoxides, thus preserving the bicyclic structure without severing the peroxide bond. This reductive trapping technique has now been extended to the hitherto unknown and unstable endoperoxide of α-pyrone *(2)*. Presently we report on the chemistry of these unusual bicyclic endoperoxides.

On photo-oxygenation of α-pyrone *(1)* in CH_2Cl_2 at 0°C using tetraphenylporphyrin as sensitizer and a General Electric 400 W sodium lamp resulted in slow consumption of the α-pyrone as monitored by subambient ^{1}H-NMR spectroscopy. After 12 h essentially all the α-pyrone had been consumed and the characteristic multiplets at δ = 5.9–6.3 and 7.0–7.5 of the 1,3-diene were replaced by broad singlets at δ = 6.80 (olefinic H) and 5.02 and 6.25 (bridgehead H). When allowed to warm up to 30°C, carbon dioxide was rapidly evolved and the above proton resonances were replaced by two multiplets at δ = 10.25 (aldehydic H) and 6.48 (olefinic H) corresponding to the signals of malealdehyde *(4)* as confirmed by an authentic sample[2]. These results suggested intervention of the novel and thermally labile cyclic peroxide *(2)* as an intermediate in the singlet oxygenation of *(1)*. We decided to isolate and purify it and confirm its structure.



Low temperature chromatography of the photo-oxygenated α-pyrone reaction mixture on silica gel at −40°C and elution with CH_2Cl_2 afforded pure *(2)*[3]. Efforts to recrystallize it at low temperature failed. Reduction of *(2)* with excess diimide in CH_2Cl_2 at −78°C[1a,4] followed by column chromatography on silica gel at −20°C and eluting with CH_2Cl_2 gave the saturated cyclic peroxide *(3)*[5]. This new compound is thermally considerably more stable than its unsaturated precursor *(2)*; decarboxylation of *(3)* to succinaldehyde on heating at 140°C was confirmed by IR and ^{1}H-NMR spectroscopy on an authentic sample.

An interesting feature of *(3)* was its emission of light during decarboxylation to succinaldehyde[6]. Thus, either *(3)* stores sufficient energy so that simultaneous peroxide bond fission and decarboxylation leads to electronically excited succinaldehyde directly or the intermediary bicyclic dioxetane *(6)* is first formed on decarboxylation of *(3)*. Subsequent ring opening of the dioxetane *(6)* would be expected to afford electronically excited succinaldehyde[7].

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CAS Registry numbers:
(1), 504-31-4; *(2)*, 65651-81-2; *(3)*, 65651-82-3; *(4)*, 3675-13-6; *(6)*, 37693-27-9; diazene, 3618-05-1

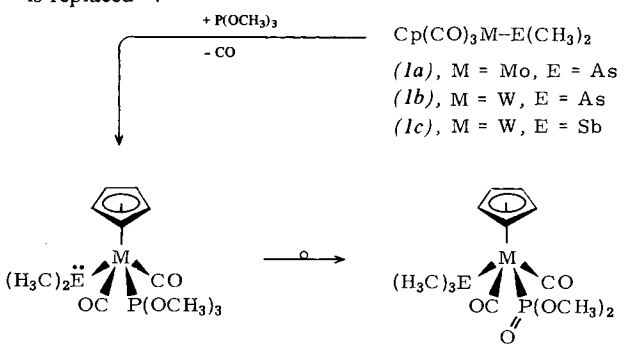
[1] a) *W. Adam, H. J. Eggelte*, J. Org. Chem. *42*, 3987 (1977); b) *W. Adam, I. Erden*, Angew. Chem. *90*, 223 (1978); Angew. Chem. Int. Ed. Engl. *17*, 210 (1978); c) *W. Adam, H. J. Eggelte, A. Rodríguez*, unpublished.
[2] *K. Alder, H. Betsing, K. Heimbach*, Justus Liebigs Ann. Chem. *638*, 198 (1960).
[3] Colorless liquid, yield 85%; ^{1}H-NMR (CCl_4, TMS): δ = 5.02 (br. s, 1H), 6.25 (br. s, 1H), 6.80 (br. s, 2H); IR (CCl_4): 1810, 1325, 1265, 1030, 960 cm^{-1}; MS: *m/e* = 128.
[4] *W. Adam, H. Eggelte*, Angew. Chem. *89*, 762 (1977); Angew. Chem. Int. Ed. Engl. *16*, 713 (1977).
[5] Colorless solid, m. p. 30°C, yield 25%; ^{1}H-NMR (CCl_4, TMS): δ = 1.85–2.60 (m, 4H), 4.45 (m, 1H), 5.78 (m, 1H); IR (CCl_4): 2950, 1800, 1340, 1300, 1180, 1050, 970 cm^{-1}; MS: *m/e* = 130.
[6] *W. Adam*, Angew. Chem. *86*, 683 (1974); Angew. Chem. Int. Ed. Engl. *13*, 619 (1974).
[7] *W. Adam*, Adv. Heterocycl. Chem. *21*, 437 (1977).

Isomerization with Methyl Migration in Trimethyl Phosphite-Arsenido and -Antimonido Complexes of Transition Metals[1]

By *Wolfgang Malisch* and *Reinhard Janta*[*]

The E atom in complexes of the type $Cp(CO)_2(PR_3)M-E(CH_3)_2$ (M = Mo, W; E = As, Sb; R = CH_3) is a center of unusually high basic activity which is manifested in a pronounced tendency to react with electrophiles[2]. The electron rich state of the E atoms is also responsible for the *irreversible isomerization* with a methyl shift from the R_3P ligand to the arsenido or antimonido function which we have observed in derivatives with R = OCH_3.

The isomerizing complexes *(2)* are accessible by reaction of the tricarbonyl precursors *(1)*[3] in benzene with equimolar amounts of trimethyl phosphite at 25°C [*(1a)*] or 50°C [*(1b)* and *(1c)*]. Under these conditions only the CO group in the *trans position* relative to the σ-bonded $(CH_3)_2E$ group is replaced[4].



(2a): m.p. 68–70°C
(2b): m.p. 80–82°C
(2c): m.p. 87°C

(3a): m.p. 152–154°C
(3b) decomp. above 167°C
(3c): m.p. 177–178°C

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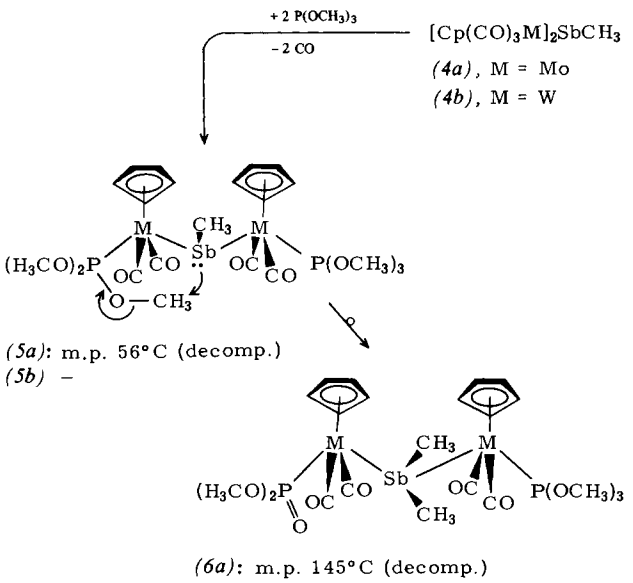
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The rearrangement *(2)*→*(3)* which is readily observed by ^{1}H-NMR spectroscopy sets in at room temperature in the presence or absence of solvent, can be thermally accelerated, and proceeds with retention at the transition metal[4]. It is complete within 7 d in the case of *(2a)* in $CHCl_3$ (0.46 M solution, 25 °C). Rate-determining factors are not only the concentration of the trimethyl phosphite complex but also the nature of its E and M atoms and the solvent polarity [k_{rel} ($CHCl_3$, 25 °C) for As:Sb = 2:1, Mo:W = 1:1.5; $CHCl_3$:C_6H_6 = 350:1]. These observations and the fact that an equimolar mixture of *(2a)* and *(2b)* rearranges just as fast as pure *(2b)* [catalytic action of *(2b)*] unequivocally indicate *intermolecular* site exchange of the methyl group.

The composition and structure of the crystalline, deep and pale yellow complexes *(2)* and *(3)*, respectively, have been confirmed by elemental analysis and mass, IR, and NMR (^{1}H, ^{13}C, ^{31}P) spectra. Compounds of the same isomeric type exhibit almost identical $\delta(^{31}P)$ and $J(^{31}P^{183}W)$ values[5]. These data are therefore very suitable for rapid identification of the isomers which differ especially in their solubility properties. Unlike *(2)*, the thermally stable rearrangement product is soluble only in polar solvents ($CHCl_3$, CH_3CN).

The O→As(Sb) methyl shift presented in this communication transforms a phosphite into a phosphonate ligand (with concomitant formation of a trimethylarsane(-stibane) ligand)[6] without assistance by alkyl halides as is generally required[7]. Compared with the few known examples of direct P=O bond formation as a result of methyl migration[8], the reaction proceeds under astonishingly mild conditions. It therefore follows that the donor strength of transition metal units endows 5B atoms with a striking ability to take over methyl groups.

In accord with this interpretation, the bismetallostibanes *(5)* accessible from trimethyl phosphite and dinuclear complexes *(4)*[9] by double *trans*-CO substitution isomerize even more readily than the systems in the monometal series, since the basic acceptor center is now exposed to the influence of *two metal donor ligands*. In the case of *(5b)*, the antimony bridge is methylated so quickly that *(5b)* itself can only be detected as an intermediate by spectroscopy.



According to the νCO absorption bands, the bridged complexes *(5)* exist in solution as a mixture of several conformers.

Experimental

(5a): $P(OCH_3)_3$ (295 mg, 2.37 mmol) is added to a solution of $[C_5H_5(CO)_3Mo]_2SbCH_3$[9] (505 mg, 0.79 mmol) in benzene (30 ml) and the mixture is stirred at room temperature for 2 h (evolution of CO!). Addition of pentane (20 ml) to the filtered solution which has been evaporated down to half its volume precipitates a solid which is washed with cold pentane (5 ml) and dried in an oil-pump vacuum; yield 756 mg (91%) of *(5a)*.

(6a): Compound *(5a)* (371 mg, 0.45 mmol) is heated in benzene (20 ml) to 60 °C for 6 h. Insoluble products are filtered off, the solvent is removed under vacuum, and the solid residue washed with pentane (4 ml); yield 302 mg (81%) of *(6a)*.

^{1}H-NMR (TMS int.): *(5a)* in C_6D_6: δC_5H_5 5.11 (d, 10H), $^3J_{HCMP}$ 1.2; δCH_3OP 3.4 (d, 18H), $^3J_{HCOP}$ 11.6; δCH_3Sb 2.4 (s, 3H). *(6a)* in $CDCl_3$: δC_5H_5 5.19 (d, 5H), $^3J_{HCMP}$ 1.2; δCH_3OP 3.29 (d, 9H), $^3J_{HCOP}$ 12.0; δC_5H_5* 5.23 (d, 5H), $^3J_{HCMP}$ 0.8; δCH_3OP 3.95 (d, 6H), $^3J_{HCOP}$ 10.8; δCH_3Sb 1.65 (s, 6H).—$^{31}P\{^1H\}$-NMR (C_6D_6, H_3PO_4 ext.): *(5a)* δ = 197; *(6a)* δ = 187, 120*.—IR (νCO in C_6H_6): *(5a)* 1919 (s), 1898 (s), 1848 (vs), 1840 (Sh), 1810 (vs) cm^{-1}; *(6a)* 1940 (Sh)*, 1929 (s), 1876 (s)*, 1855 (Sh) cm^{-1} (*absorptions of the $Cp(CO)_2M$—$P(O)[OMe]_2$ group).

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[1] Transition Metal Substituted 5B Element Systems, Part 20. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 19: *W. Malisch, P. Panster*, Chem. Ber., in press.
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[4] The *trans* configuration of the complexes *(2)* and *(3)* is confirmed by the intensity ratio $\nu CO_{sym}/\nu CO_{asym}$ (>1) and the appearance of a single CO resonance with $^2J_{CMP}$ = 25–37 Hz in the $^{13}C\{^1H\}$-NMR spectra.
[5] $\delta(^{31}P)/J(^{31}P^{183}W)$ [rel. H_3PO_4 ext./Hz]: phosphite complexes (C_6D_6) *(2b)* 160/460, *(2c)* 159/480, *(5b)* 159/430; phosphonate complexes ($CDCl_3$) *(3b)* 84/317, *(3c)* 82/325, *(6b)* 90/347 [149/419 $(CH_3O)_3P$—*W*].
[6] Isomerization is accompanied by formal exchange of donor properties of the two 5B element atoms towards the metallic center:
one-electron donor $\underset{P}{\overset{As(Sb)}{\rightleftharpoons}}$ two-electron donor.
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Tetraphenylphosphonium Tetrakis(difluorooxosulfimidato)borate[**]

By *Rainer Eisenbarth* and *Wolfgang Sundermeyer*[*]

We wish to report the synthesis of the tetraphenylphosphonium salt of tetrakis(difluorooxosulfimidato)borate *(3)*, the first coordination compound containing only $NSOF_2$ groups as ligands. Along with $Li[B(N_3)_4]$[1] and $Li[B(NCS)_4]$[2], *(3)* constitutes a further example of a tetra-

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coordinated pseudohalide complex of boron linked *via* nitrogen.

$$(C_6H_5)_4P[NSOF_2] + B(NSOF_2)_3 \rightarrow (C_6H_5)_4P[B(NSOF_2)_4]$$
(1) *(2)* *(3)*

When tetraphenylphosphonium difluorooxosulfimidate *(1)*[3] (0.44 g, 1.0 mmol) and boron tris(difluorooxosulfimidate) *(2)*[4] (2 g, 6.4 mmol) are condensed together in a glass trap at −80 °C and the product mixture is allowed to warm to room temperature over 12 h, stirred for a further 5 to 6 h and the excess of *(2)* removed by pumping (48 h), *(3)* is obtained in quantitative yield as a white crystalline solid whose X-ray diagram differs from that of *(1)* and whose elemental analysis proves it to be pure *(3)*. The ^{1}H-NMR spectrum is compatible with that of *(1)* and of $(C_6H_5)_4PCl$; the ^{19}F-NMR spectrum shows a singlet at $\delta = -51.8$ (in acetonitrile, rel. $CFCl_3$ ext.). Together with the IR spectrum (3028 w, 1590 m, 1450 vs, 1342 w, 1320 w, 1260 s, 1192 m, 1113 s, 1003 m, 940 vs, 785 vs, 756 m, 728 vs, 695 s, 590 m, 560 m and 530 s cm^{-1}; KBr pellet) the ^{11}B-NMR spectrum, in particular, with a signal at $\delta = 7.96$ (in $[D_3]$-acetonitrile, rel. $BF_3 \cdot OEt_2$ ext.), provides evidence for the tetracoordination of the boron. This experimental value corresponds to that expected according to a Scheme described by *Nöth* and *Vahrenkamp* for the chemical shift as a function of the electronegativity of the ligand atoms X in $BX_4^{\ominus}$ complexes[5].

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(1), 14872-92-5; *(2)*, 38998-35-5; *(3)*, 65749-23-7

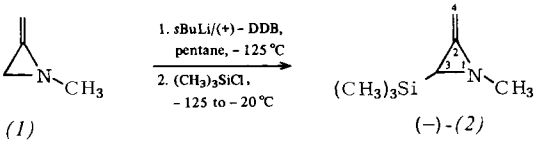
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Enantioselective Synthesis and Thermal Reorganization of an Optically Active Methyleneaziridine[**]

By *Helmut Quast* and *Carlos A. Weise Vélez*[*]

The routine application of conclusions reached for hydrocarbons to the corresponding hetero systems can be inadmissible in the case of strongly perturbed pericyclic reactions[1]. While the thermal isomerization of methylenecyclopropanes is known to be largely stereospecific with inversion at the migrating carbon atom[2], nothing is known about the stereochemistry of the thermal reorganization of heteromethylenecyclopropanes apart from the racemization of optically active 2,3-di-*tert*-butylcyclopropanone[3a] and the rearrangement of optically active allene oxide intermediates[3b]. We have now found that the methyleneaziridine—cyclopropanimine rearrangement[4] also proceeds stereospecifically.

The optically active methyleneaziridine *(−)-(2)* could be synthesized in 36—48% yield by lithiation of *(1)*[5] using 1.08 equivalents of *sec*-butyllithium in pentane at −125 °C in the presence of 9.10 equivalents of *(S,S)*-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane [(+)-DDB] as auxiliary chiral agent[6] and subsequent reaction with 1.05 equivalents of chloro(trimethyl)silane at −125 to −20 °C. Enantioselective metalations have hitherto rarely been observed[7].



(1) *(−)-(2)*

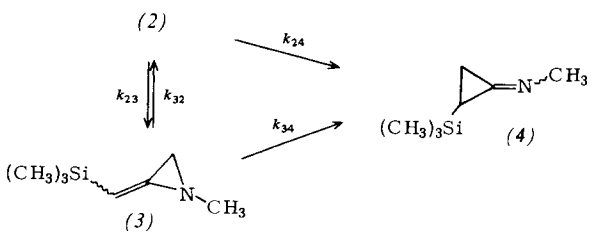
After repeated fractional distillation in a 20-cm Spaltrohr® column (b.p. 52.5 °C/75 torr), *(−)-(2)* proved to have a purity of 98% (GC) and a specific rotation of $[\alpha]_{405}^{20} = -86.27°$ ($[(-)-(2)] = 0.348$ mol/l in $[D_6]$-benzene). Integration of the trimethylsilyl ^{1}H-NMR signals in benzene using Pr(facam)$_3$[8] as shift reagent revealed an enantiomer excess of 12.4±1%.

Solutions of *(2)* in $[D_6]$-benzene were heated in sealed NMR sample tubes previously treated with *O,N*-bis(trimethylsilyl)acetamide and degassed at 10^{-5} torr. In the case of racemic *(2)* the thermolysis was monitored ^{1}H-NMR spectroscopically on *a single* sample by measurement of the trimethylsilyl signals, while in the case of *(−)-(2)* *nine* identical samples were firstly measured ^{1}H-NMR spectroscopically and then polarimetrically at 405 nm under strict exclusion of moisture. At 120.0 °C thermolysis of *(2)* afforded the diastereomeric methyleneaziridines *(3)* and cyclopropanimines *(4)* in the constant isomeric ratios *(E)-(3)*:*(Z)-(3)* = 86:14 and *(E)-(4)*:*(Z)-(4)* = 56:44, respectively. Decomposition of *(4)* into methyl isocyanide and trimethylsilylethene[4] was not observed at 120 °C but only at 140 °C and above, albeit to a small extent. However, at 120 °C unknown secondary products of *(4)* were very slowly formed (trimethylsilyl singlets at $\delta_H = 0.05$, 0.11, 0.29), which after 24 h only amounted to 6—10% of the total product mixture and were added to *(4)* in the kinetic evaluation.

The structures of *(2)* and its rearrangement products *(3)* and *(4)* follow from the IR and ^{1}H-NMR spectra (Table 1). IR ($\tilde{\nu}$, cm^{-1}) *(2)*: 1790, 1760 (gas phase); *(3)*: 1735, *(4)*: 1773 (both in C_6D_6). ^{1}H-NMR (C_6D_6; δ_H) *(E)-(4)*: −0.08 ($(CH_3)_3Si$); *(Z)-(4)*: −0.02 ($(CH_3)_3Si$). Both diastereomeric cyclopropanimines *(4)* show overlapping multiplets at δ_H = 0.3—1.5 and 3.2—3.3 belonging to two $ABCX_3$ systems. In the case of *(3)* the configuration was determined on the basis of the allyl coupling constants, while in the case of *(4)* the predominant diastereomer was assigned the *(E)*-configuration. Noteworthy is the coupling constant of $^4J = 0.4$ Hz between 3-H and the *N*-methyl group of *(2)* which, with this order of magnitude, is obviously observable only if the *trans* invertomer predominates.

Owing to the irreversibility of the rearrangement to cyclopropanimines[9] and the constant *E*:*Z* ratios in the case of both *(3)* and *(4)*, four rate constants were sufficient for the description of the thermal reorganization of *(2)*. Starting

Scheme 1:



from approximate values, obtained from initial data of the thermolysis of *(2)* and of a 5:95 mixture of *(2)* and *(3)*, by

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Table 1. ^{1}H-NMR data for the methyleneaziridines in [D$_6$]-benzene.

Cpd.	Chemical shifts δ_H					Coupling constants $\|J\|$ [Hz]			
	NCH_3	3-H	3-R^1	4-R^2	4-R^3	^2J	$^4J_{cis}$	$^4J_{trans}$	$^5J_{trans}$ [a]
(1) [b]	2.41	1.885		H 4.559	H 4.579	1.15	0.85	1.32	< 0.1
(2)	2.39 [c]	0.95	$(CH_3)_3Si$ 0.07	H 4.54	H 4.66	1.11	1.35	1.90	*ca.* 0.1
(E)-(3)	2.26	1.75		$(CH_3)_3Si$ 0.16	H 4.980	—	—	1.1	—
(Z)-(3)	2.32	1.64		H 4.975	$(CH_3)_3Si$ 0.22	—	0.7	—	*ca.* 0.1

[a] Estimated from the broadening of the signals of $R^2 = H$ and the *N*-methyl groups.
[b] In CCl_4; the data of the ABX_2 system were optimized using the program LAOCOON III [9].
[c] $^4J_{(3\text{-}H,N\text{-}CH_3)} = 0.4$ Hz.

means of a program developed for the computation and drawing of mol fraction—time curves based on the solutions of the differential equations corresponding to Scheme 1[10], we obtained the optimized constants listed in Table 2.

Table 2. Rate constants of the thermal reorganization of methyleneaziridine *(2)* according to Scheme 1 in [D$_6$]benzene at 120.0°C.

Thermolysis of	Rate constants × 10^5 [s^{-1}]			
	k_{23}	k_{32}	k_{24}	k_{34}
racemic *(2)* [a]	6.20	0.36	2.80	0.165
(−)-(2) [b]	5.90	0.37	3.60	(0.02)

[a] One sample consisting of 0.063 ml of *(2)* in 0.520 ml of [D$_6$]benzene + 0.010 benzene.
[b] Nine identical samples; $[(-)\text{-}(2)] = 0.348$ mol/l.

Table 2 shows satisfactory agreement between the data obtained in different ways. The trimethylsilyl group at the double bond stabilizes *(3)* by 9.2 kJ/mol compared to *(2)*. From the rate constants it can be estimated that initially very little *(4)* is formed (after 10 h only 4%, total 30—35%) *via* achiral *(3)* and that only negligible racemization of *(−)-(2)* occurs in this way.

In the thermolysis of *(−)-(2)* the mol fractions $x(i)$ after 10 h were: $x(2) = 0.06$, $x(3) = 0.56$, $x(4) = 0.35$ and x(secondary products of *(4)*) = 0.03. But α_{405} had only decreased from $\alpha_0 = -4.330°$ to $-2.03°$ [path length = 10 cm]. *(4)*, and thus also the optically active species, was selectively and completely removed *without altering any of the other components* (IR and ^{1}H-NMR spectra) by treating a sample of *(−)-(2)* [$x(4) = 0.35$, $\alpha_{405} = -1.720°$], previously heated for 22.6 h, with water. Consequently, only *(4)* was optically active and, like the educt *(−)-(2)*, levorotatory; however, the enantiomer excess of *(−)-(4)* could not be determined. Assuming that no direct racemization[3a] of *(−)-(2)* takes place, the maximum possible contribution to α_{405} arising from *(−)-(2)* can be calculated according to $\alpha_{(2)} = \alpha_0 \exp -(k_{23} + k_{24})t$. Thus, for *(−)-(4)* a minimum rotation of $\alpha_{(4)} = (\alpha - \alpha_{(2)})/x(4) = -5.59 \pm 0.15°$ (from 5 measurements during the first 5 h, $[(-)\text{-}(4)] = 0.348$ mol/l in [D$_6$]-benzene) is obtained, which is considerably greater than the initial value α_0 and therefore indicative of a high degree of stereospecificity for the methyleneaziridine—cyclopropanimine rearrangement. Since on geometrical grounds retention at the migrating carbon atom, C-3 in *(2)*, is highly improbable, inversion must have occurred as in methylenecyclopropanes[2].

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CAS Registry numbers:
(1), 25012-55-9; *(−)-(2)*, 65665-40-9; *(±)-(2)*, 65665-41-0; *(E)-(3)*, 65665-42-1; *(Z)-(3)*, 65665-43-2; *(E)-(−)-(4)*, 65665-44-3; *(Z)-(−)-(4)*, 65665-45-4; (+)-BDB, 26549-21-3

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[10] The solutions quoted by *E. S. Lewis* and *M. D. Johnson*, J. Am. Chem. Soc. *82*, 5399 (1960), contain errors. We thank Dipl.-Math. *S. Stindl* and Dipl.-Chem. *M. Heuschmann* for correcting these and Dr. *W. Risler* for writing the computer program.

Difluoroarsoranes and Homologous Compounds $R'R_2EF_2$ (E = As, Sb, Bi) by Oxidative Direct Fluorination of Organoarsanes, Organostibanes, and Organobismuthanes[**]

By *Ingo Ruppert* and *Volker Bastian*[*]

Selective gas phase fluorinations of organoelement compounds are comparatively rarely exploited reactions in preparative chemistry[1]. The observed oxidative fluorination of the phosphorus in tertiary phosphanes[2] without significant formation of side-products has now been extended for the first time to its higher homologs.

$$Ph_2E\text{–}R + F_2 \xrightarrow{CFCl_3} \underset{\displaystyle F}{\overset{\displaystyle F}{Ph_2E}}\text{–}R$$

(1) *(2)*

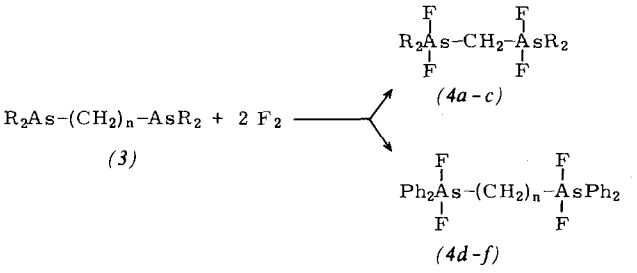
E = As: R = Me*(a)*, Ph*(b)*;
E = Sb: R = Me*(c)*, Ph*(d)*;
E = Bi: R = Ph*(e)*

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[**] Fluorinated Organoelements: Oxidative Liquid-Phase Direct Fluorination, Part 3.—Part 2: *I. Ruppert*, Chem. Ber., in press.

Surprisingly, despite the decreasing strength of the E—C bond on going from P to Bi, not only the usual competition from side-chain halogenation but even fluorinating cleavage of the element-carbon bond can be largely suppressed under the mild reaction conditions[3].

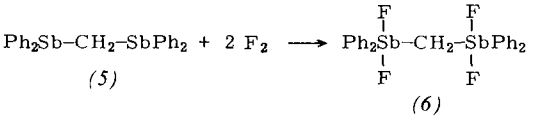
Direct fluorination simplifies the conventional two-step chlorine/fluorine exchange with metal fluorides [*(2d)*[4a], *(2e)*[4b]] and is preparatively comparable with the fluorination by sulfur tetrafluoride[4c] previously described only for *(2b)*. Its wide range of application can be illustrated using as example the bis(difluoroarsoranes), a previously unknown class of substances.



(3) *(4a-c)* *(4d-f)*

n = 1: R = Me*(a)*, Et*(b)*, *i*Pr*(c)*, Ph*(d)*;
n = 2: R = Ph*(e)*;
n = 3: R = Ph*(f)*

Both phenylated and the more readily substituted alkylated ditertiary bisarsanes *(3)* containing methyl bridges of varying lengths can be converted in good yields into their tetrafluorides by a stream of fluorine diluted with an inert gas. The bisstibane *(5)* reacts similarly.

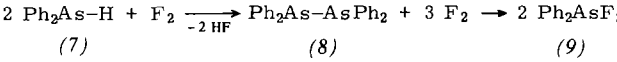


(5) *(6)*

Depending on the substrate reactivity and the solubility of the partially fluorinated intermediates only part of the fluorine passed into the system will actually be consumed. On the other hand, uncontrolled over-fluorination attacks the alkyl moiety non-specifically[5]; hence, it is necessary to use well defined amounts of fluorine.

In the case of *(3b)* and *(3c)* the reaction course is difficult to monitor by ^{1}H-NMR spectroscopy because of the high proportion of phenyl or complex alkyl signals[6]. Educt, difluoride intermediate[7], and product, however, can easily be detected by $^{13}C\{^1H\}$-NMR spectroscopy; it not only guarantees recognition of the reaction end-point (shift parameters in Table 1), but also permits a simple structural diagnosis based on fluorine-carbon coupling constants. Thus, the pseudotriplet of the α-alkyl C atom or the triplet of the α,β-phenyl C atoms and the quintet splitting of the monomethylene bridge afford proof that two F atoms coordinate each As center. This constitution also applies—at least in solution—in the case of the methylated parent compound *(4a)*, though its physical properties (higher melting point, lower solubility) in comparison with *(4b—d)* is surprising[8]. A fluorine exchange caused by traces of hydrogen fluoride, which leads to merging of the significant couplings to a broad singlet, can be suppressed by carrying out the measurement at low-temperature or, more simply, by addition of a little triethylamine.

Attempts to fluorinate the arsanes *(7)* or *(8)* without rupturing the As—H or As—As bond have so far failed. Instead, the trifluorodiphenylarsorane *(9)*[9] was obtained from the hydride *via* the isolable intermediate *(8)*.



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

Experimental

A stream of diluted fluorine (max. 20 ml F_2 to 100 ml Ar per min) is passed into a magnetically stirred solution of 30 mmol *(1a—e)*, *(3a—f)* or *(5)*[10] in 150—200 ml anhydrous $CFCl_3$ (Solidex-glass flask with delivery tube and fitted with a multiple-coil condenser, −90 °C circulatory cooling). Only in the case of *(3a—c)* is the reaction solution additionally cooled to −78 °C. As shown by $^{13}C\{^1H\}$-NMR monitoring, the reaction is complete only after addition of a 2- to 2.5-fold excess of fluorine; however, excessive over-fluorination must be avoided in the preparation of the alkylated bis(difluoroarsoranes) *(4a—c)*. Workup of the products depends upon their solubility in $CFCl_3$: In the case of *(4b, c)* the $CFCl_3$ is first removed and the remaining viscous

Table 1. Preparative and NMR spectroscopic data [a] of the compounds synthesized.

	Yield [b] [%]	M.p. [°C] B.p. [°C/torr]	^{19}F-NMR [c]	$^{13}C\{^1H\}$-NMR [c] R = Alkyl		Bridge	Phenyl			
				C—EF_2	C—CEF_2	F_2E—C	C^1	C^2	C^3	C^4
(2a)	75	96	− 78.0 q (7.0) [d]	22.7 t (21.5)			136.9 t (16.1)	132.7 t (6.6)	129.0 s	131.9 s
(2b)	93	135	− 88.9 s				137.4 t (18.3)	133.0 t (7.0)	129.1 s	131.9 s
(2c)	74	92	−137.1 q (5.0)	11.0 t (16.7)			133.6 t (13.8)	135.3 t (5.0)	129.5 s	132.2 s
(2d)	88	116	−153.2 s				134.3 t (15.4)	135.4 t (4.9)	129.6 s	132.2 s
(2e)	78	158	−161.3 s				153.7 s [e]	134.3 s	131.4 s	131.9 s
(4a)	82	166	− 46.3 s	23.0 pt (18.0) [f]		45.5 quint (22.0)				
(4b)	82	106/0.001	− 72.2 s	32.1 pt (15.5)	8.0 s	40.7 quint (22.5)				
(4c)	40	118/0.001	− 89.0 s	42.9 pt (15.0)	18.5 t	36.9 quint (23.4)				
(4d)	73	134	− 74.1 t (10.0)			48.9 quint (25.6)	136.7 t (15.5)	133.3 t (7.8)	128.9 s	132.0 s
(4e)	88	144	− 89.9 s			34.8 tt (20.7, 4.8)	135.8 t (16.0)	133.4 t (7.5)	129.1 s	132.1 s
(4f)	63	108	− 88.8 t (10.0)		19.1 s	40.3 t (18.0)	136.3 t (15.0)	133.3 t (6.0)	129.0 s	131.9 s
(6)	91	153	−127.7			27.4 quint (21.0)	134.1 t (13.5)	135.1 t (4.5)	129.6 s	132.3 s

[a] The ^{19}F- (Varian A 56/60, 56,4 MHz, $CFCl_3$ int.) and $^{13}C\{^1H\}$-NMR spectra (Bruker WP60, 15.08 MHz, TMS int.) were recorded in concentrated $CDCl_3$ solution. The less informative ^{1}H-NMR spectra, which show ^{13}C-analogous fluorine couplings in the alkyl part, are available from the author on request. [b] Analytically pure product; with the exception of *(2e)* all reactions proceed almost quantitatively (^{13}C-NMR). [c] δ (*J* [Hz]). [d] Superposed ^{1}H-^{13}F coupling of the alkyl(ene) protons in Hz; the fluorine signals given as singlets (s) are broadened by nuclear quadrupole and complex proton interaction. [e] Despite high resolution no triplet observable. [f] Pseudotriplet (pt) due to $^2J(F—As—C)$ and $^4J(F—AsCAs—C)$; first order coupling constant.

residue is distilled *in vacuo* (mercury vapor jet pump). In the case of *(2a, c, d)* the solution is first filtered free of small amounts of solid byproducts, the $CFCl_3$ removed, and the residue then recrystallized from hot *n*-hexane [*(2a, d)*] or frozen out from *n*-pentane [*(2c)*]. In all the remaining cases the almost colorless suspension is first evaporated down *in vacuo* and the residue then recrystallized from boiling *n*-heptane [*(2b, e), (4d—f)*], benzene [*(4a)*], or cyclohexane [*(6)*] under an inert gas.

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German version: Angew. Chem. *90*, 226 (1978)

CAS Registry numbers:
(1a), 945-48-2; *(1b)*, 603-32-7; *(1c)*, 30982-88-8; *(1d)*, 603-36-1; *(1e)*, 603-33-8; *(2a)*, 33756-92-2; *(2b)*, 3824-71-3; *(2c)*, 33756-92-2; *(2d)*, 373-84-2; *(2e)*, 2023-48-5; *(3a)*, 30043-88-0; *(3b)*, 65718-97-0; *(3c)*, 65718-96-9; *(3d)*, 21892-63-7; *(3e)*, 4431-24-7; *(3f)*, 19364-57-9; *(4a)*, 65718-95-8; *(4b)*, 65718-94-7; *(4c)*, 65718-93-6; *(4d)*, 65718-92-5; *(4e)*, 65718-91-4; *(4f)*, 65718-90-3; *(5)*, 30224-53-4; *(6)*, 65718-89-0; *(7)*, 829-83-4; *(8)*, 2215-36-3; *(9)*, 65794-25-4; ^{13}C, 14762-74-4

[1] On the problems of elemental fluorination cf. *E. K. S. Liu, R. J. Lagow*, J. Am. Chem. Soc. *98*, 8270 (1976).
[2] *I. Ruppert, V. Bastian*, Angew. Chem. *89*, 763 (1977); Angew. Chem. Int. Ed. Engl. *16*, 718 (1977).
[3] In contrast, alkylarsanes are already cleaved at moderate temperatures by Cl_2, Br_2 or I_2; this halodemetalation of the alkyl moiety has recently been developed into a new synthetic method: *T. Kauffmann, H. Fischer, A. Woltermann*, Angew. Chem. *89*, 52 (1977); Angew. Chem. Int. Ed. Engl. *16*, 53 (1977).
[4] a) *G. O. Doak, G. G. Long, L. D. Freedman*, J. Organomet. Chem. *4*, 82 (1965); b) *F. Challenger, J. F. Wilkinson*, J. Chem. Soc. *121*, 91 (1922); c) *W. C. Smith*, J. Am. Chem. Soc. *82*, 6176 (1960).
[5] Accordingly, in the spectra of *(4a—c)* higher fragmentations of low intensity are also observed which derive from molecular ions $M^+ + n\,18$ $(= M^+ - nH + nF;\ n = 1, 2)$.
[6] These are caused by additional ^1H-^1H coupling of diastereotopic methylene-[*(3b)*] and methyl protons [*(3c)*].
[7] Apart from the expected $^{13}C\{^1H\}$-NMR spectrum, with a triplet for the α-C atoms of the difluoroarsorane moiety with slight deshielding of the dialkylarsane moiety, the difluoride intermediate can be recognized by its ^{19}F-NMR signal, which is shifted upfield by about 5 ppm compared to that in *(4a—d)*.
[8] This finding points to an isomeric fluoroarsonium trifluoroarsenate structure in the solid state.
[9] At room temperature *(9)* shows a trigonal-bipyramidal array of differently fixed fluorine atoms: ^{19}F-NMR ($CDCl_3$): $\delta = -72.3$ [d, $^2J(F_e - F_a) = 73$ Hz, F_a], -94.9 [t, F_e], as previously found by *E. L. Muetterties, W. Mahler, K. J. Packer, R. Schmutzler*, Inorg. Chem. *3*, 1298 (1964). Thus, the more recent findings on a non-freezable ligand exchange [*L. B. Littlefield, G. O. Doak*, J. Am. Chem. Soc. *98*, 7881 (1976)] could not be confirmed.
[10] Preparation of starting compounds: *(1a)*: *G. J. Burrows, E. E. Turner*, J. Chem. Soc. *1920*, 1373; *(1b)*: *R. L. Shriner, C. N. Wolf*, Org. Synth. Coll. Vol. *IV*, 910 (1963); *(1c)*: as in *K. Bowden, E. A. Braude*, J. Chem. Soc. *1952*, 1068 [$b.p._{0.001}$ 98 °C]; *(1d, e)*: *H. E. Ramsden*, Brit. Pat. 824944 (1959), Metal and Thermit Corp. [Chem. Abstr. *54*, P 17238 d (1960)]; *(3a—d)*: Grignard reaction of methylenebis(dichloroarsane) [*F. Popp*, Chem. Ber. *82*, 152 (1949)] in ether (RBr: $(Cl_2As)_2CH_2 = 5:1$) [*(3a)*: $b.p._{14}$ 56 °C (64 % yield), *(3b)*: $b.p._{14}$ 117 °C (85 %), *(3c)*: $b.p._{0.01}$ 74 °C (63 %); *(3d)*: *A. J. Titor, B. B. Lewin*, Chem. Abstr. *49*, 4504 h (1955)]; *(3e, f)*: *A. Tzschach, W. Lange*, Chem. Ber. *95*, 1360 (1962); *(5)*: *Y. Matsumura, R. Okawara*, J. Organomet. Chem. *25*, 439 (1970).

ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

The structure and properties of amorphous ("glassy") metals and alloys are reviewed in an article by *P. Chaudhari* and *D. Turnbull*. Certain metals and alloys can be put into the glassy form by quenching the melt to $T < T_g$, condensation of the gas or diluted solution onto a substrate kept at $T < T_g$, or radiation of the crystalline solid at $T < T_g$ (T_g = glass transition temperature). The electrical, magnetic, and mechanical properties as well as the superconductivity of various metallic glasses including, *inter alia*, those of Ge, Zr, Hf, Ir, Os, Ru, and of Co/P, Cu/Cr, Ni/Nb, and Gd/Co alloys are discussed and their technical potential outlined. [Structure and Properties of Metallic Glasses. Science *199*, 11—21 (1978); 114 references]

[Rd 998 IE]

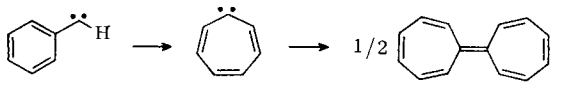
Transition-metal thiocarbonyls and selenocarbonyls form the subject of a review article by *I. S. Butler*. Compounds containing the CS ligand can be obtained by direct reaction with CS_2 (example: $RuBr_3(PPh_3)_2 \cdot MeOH \rightarrow RuBr_3(CS)(PPh_3)$), reaction with CS_2/PPh_3 ($[IrCl(C_8H_{12})]_2 \rightarrow$ *trans*-$IrCl(CS)(PPh_3)_2$), treatment with thiophosgene, or with *O*-esters of chlorothiocarbonic acid. The CSe ligand can be similarly inserted. CS can also function as bridge ligand; the corresponding CSe complexes have so far not been reported. Only very few complexes containing multiple CS or CSe ligands are known, in contrast to CO complexes. [Transition-Metal Thiocarbonyls and Selenocarbonyls. Acc. Chem. Res. *10*, 359—365 (1977); 73 references]

[Rd 1000 IE]

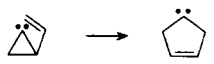
Transfer RNA is the topic to which a complete issue of Accounts of Chemical Research has been devoted. After an introduction by *A. Rich* and *P. R. Schimmel* (pp. 385—387; 24 references), *A. Rich* reviews the three-dimensional structure and biological function of tRNA (pp. 388—396; 29 references). *B. R. Reid* and *R. E. Hurd* deal with NMR investigations (pp. 396—402; 34 references) and *J. A. McCloskey* and *S. Nishimura* with modified nucleosides in tRNA (pp. 403—410; 101 references). *P. R. Schimmel* reports on the recognition process between tRNA and aminoacyl-tRNA synthetase (pp. 411—418; 49 references) and *W. H. McClain* on the terminal seven steps of the biosynthetic pathway leading from DNA to tRNA (pp. 418—425; 29 references). [Acc. Chem. Res. *10*, No. 11 (1977)]

[Rd 1 IE]

Carbene-carbene rearrangements in solution are reviewed by *W. M. Jones*. In such reactions the carbene initially formed is first converted into a second carbene, which then yields products containing only tetravalent carbon. In rearrangements of Type I (only these are described) the "divalency" formally shifts from the carbene carbon to another carbon atom. Rearrangements of Type II are limited (with one excep-



(I)



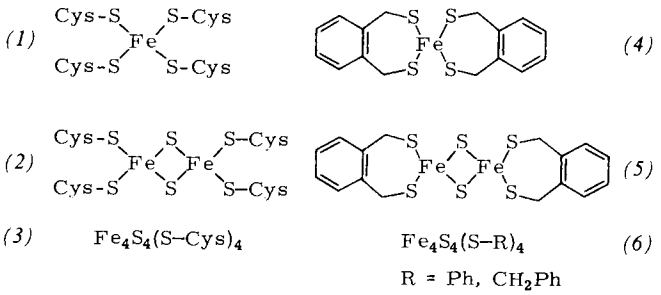
(II)

tion) to rearrangement of vinylcyclopropylidenes to cyclopentylidenes. Here, the same carbon atom functions as carbene carbon atom before and after the rearrangement. [Carbene-Carbene Rearrangements in Solution. Acc. Chem. Res. *10*, 353—359 (1977); 32 references]

[Rd 999 IE]

Synthetic approaches to the active sites of iron-sulfur proteins is the title of an article by *R. H. Holm*. Studies on synthetic analogs can, *inter alia*, lead to recognition of the smallest structural unit which exhibits the properties of the natural protein, and the influence of the "biological" matrix on the Fe—S coordination unit can be investigated. So far four types of coordination units have been demonstrated in Fe—S proteins; three of these are *(1)*, *(2)*, and *(3)* (having a cubane-like molecular skeleton), whose structurally characterized synthetic analogs are *(4)* to *(6)*. (The charges of the structural units have been omitted.) [Synthetic Approaches to the Active Sites of Iron-Sulfur Proteins. Acc. Chem. Res. *10*, 427—434 (1977); 74 references]

[Rd 2 IE]



(1)

(2)

(3) $Fe_4S_4(S\text{–}Cys)_4$

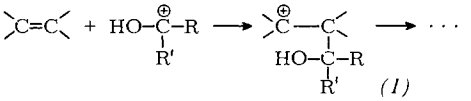
(4)

(5)

(6) $Fe_4S_4(S\text{–}R)_4$

R = Ph, CH_2Ph

The Prins reaction, *i.e.* the reaction of alkenes with aldehydes in the presence of an acid catalyst, is the theme of an article by *D. R. Adams* and *S. P. Bhatnagar*. Depending on the conditions the Prins reaction leads to 1,3-dioxanes, 1,3-diols, unsaturated alcohols and/or their secondary products; they can



(1)

all be derived from the cation *(1)*. By careful choice of reaction conditions it is possible to obtain a major product in good yields instead of the usual complex mixture of products. [The Prins Reaction. Synthesis *1977*, 661—672; 94 references]

[Rd 4 IE]

BOOK REVIEWS

Ullmanns Encyklopädie der technischen Chemie (Ullmann's Encyclopedia of Industrial Chemistry). Edited by *E. Bartholomé*, *E. Biekert*, *H. Hellmann*, *H. Ley* (deceased) and *W. M. Weigert* (deceased). Vol. 12: Fungicides to Hydroxylamine. Verlag Chemie GmbH, Weinheim–New York 1976. 4th edit., xvi, 727 pp., 304 figs., 185 tables, half leather, DM 430.00.

This is the sixth alphabetical part of the fourth edition[*]. A characteristic that is particularly noticeable in this volume is the large number of technologically oriented entries, exemplified by topics of applied electrochemistry such as galvanic cells (63 pages, including a section on fuel cells), electroplating (67 pages), and semiconductors (31 pages), by agricultural topics such as cereals and cereal products (17 pages), animal feedstuffs (25 pages), fungicides (14 pages), and herbicides (19 pages), and by soft drinks (26 pages). Further entries from the field of technology are those dealing with floor coverings (18 pages), antifreezes (6 pages), hair preparations (29 pages), skin cosmetics (11 pages), and most entries on wood (altogether 60 pages). In addition, most of the other entries also contain technological data. This shows that the new "Ullmann" gives a more complete coverage of industrial chemistry than did the previous editions. This of course includes problems of the environment and questions of safety in the preparation and use of chemicals.

The following entries may be mentioned from the field of inorganic chemistry: gallium, germanium, gold, hafnium (including their important compounds and—in the case of gold—alloys), hard metals, glass and glass ceramics (50 pages), plaster (27 pages), and the following entries from the field of metal processing: casting (17 pages) and cast iron (7 pages). Organic chemistry is represented by entries on furan, glycerol, guanidine, urea (18 pages), gelatin (10 pages), natural and synthetic resins (altogether 31 pages), and fuel oils (27 pages), and pharmaceutical chemistry by an entry on cardiovascular preparations (46 pages).

As in the previous volumes, the treatment is clear, concise, and sound. There are many cross references, both in the text and by the entries treated elsewhere (*e.g.* at the entry "Yeasts", we find the reference "see under Proteins").

It should be stressed, in conclusion, that there is no other work giving such detailed description of industrial chemistry as a whole.

Ulfert Onken [NB 399 IE]

Interpretation of Carbon-13 NMR Spectra. By F. W. *Wehrli* and *T. Wirthlin*. Heyden. London–New York–Rheine 1976. 1st Edit., xvi, 310 pp., bound, DM 59.50.

There are already many standard works on ^{13}C-NMR spectroscopy which, however, serve mainly as data compilations: the present work is really the first *textbook* on the subject, and thus fills a gap.

The "Basic Principles" give the usual introduction and a description of instruments (21 pages, 23 references). It is a little difficult to understand why the authors do not mention quadrature phase detection, offered by two spectrometer manufacturers, when they discuss the folding of spectra on two pages. The next chapter, "The Spectral Parameters" (42 pages, 92 references) consists of tabulated data. All the incremental systems used for the calculation of substitution effects are presented clearly. Regrettably, the latest views on the way the γ-effect operates (p. 28) could not be incorporated. The third chapter, "Assignment Techniques" (65 pages, 105 references), deals predominantly with the various recording

[*] Cf. Angew. Chem. Int. Ed. Engl. *16*, 202 (1977).

techniques by which the problems of assignment can be solved. Particularly useful is the section entitled "Second Order Effects in Off-Resonance Spectra", in which the authors explain why off-resonance spectra exhibit unusual splitting in certain cases. The fourth chapter, "Nuclear Spin Relaxation" (23 pages, 33 references), gives a very concise account of ^{13}C spin relaxation, which differs from the otherwise less theoretical approach used in the book. However, the statement that ^{13}C-NMR signals relax with a single exponential time constant (p. 129) is true for methylene and methyl groups only if the cross correlation is ignored.

Chapter 5, "Applications" (124 pages, 136 references), constitutes the main part of the book and will soon find its way into courses on ^{13}C resonance spectroscopy. The principles given elsewhere in the book can here be put into practice in numerous aptly chosen exercises, some of which relate to polymers and biopolymers. The solutions to these exercises are discussed in detail in an Appendix. This chapter could be even more useful if it had a better layout. There is only a subject index, but that contains all the important entries.

An altogether successful, high quality book, essential for libraries and recommended as a manual to those who deal routinely with ^{13}C-NMR spectra.

Stefan Berger [NB 400 IE]

Organic Chemistry of Drug Synthesis. By *D. Lednicer* and *L. A. Mitscher*. John Wiley and Sons, New York–London 1977. 1st Edit., xvii, 471 pp., bound, £ 16.90.

This book is intended for undergraduates studying medicinal chemistry (where this is offered as a course), pharmaceutical chemists, and organic chemists interested in medical problems. After a short introduction, the authors describe in 21 chapters (432 pages) the synthesis and biological action of common drugs tested and/or used in the United States. The book differs from comparable accounts in that, apart from the chapter on local anesthetics, the chemical structure forms the basis of the classification and discussion of the pharmacological action. More specifically, we can learn here *e.g.* about prostaglandins, steroids, tetracyclines, morphine derivatives, benzodiazepines, phenothiazines, β-lactam antibiotics, benzyl and benzhydryl derivatives, phenethyl- and phenylpropylamines, arylacetic and arylpropanoic acids, arylethenes, monocyclic and polycyclic arenes, acyclic compounds, and heterocyclic compounds with five- or six-membered (condensed) rings. The book ends with a 15-page Cross Index of Drugs and an 8-page Glossary of the relevant terms. The literature is covered up to 1971/72, and in some cases up to 1974.

Though compact, the work is often stimulating and can be considered to complement the standard works of *Burger* and *Ehrhart-Ruschig*, to which one should turn for a more detailed study, even according to the authors of this book. A particular shortcoming of the latter is that the chemical formulas are often numbered wrongly.

Bernard Unterhalt [NB 403 IE]

Applications of Biochemical Systems in Organic Chemistry. Vol. 10. Edited by *J. B. Jones*, *C. J. Sih*, and *D. Perlman*. John Wiley and Sons, New York–London 1976. Part I: 1st Edit., xii, 505 pages, bound, £ 24.25. Part II: 1st Edit., x, pages 506–1065, bound, £ 26.65.

Part I was written by the editors and three other authors, and Part II by 14 authors; These are either organic chemists with special interest in enzyme catalysis and particularly its steric aspects, or biochemists sailing close to chemistry. Since most organic chemists still largely ignore techniques of biological nature, this work is not without certain missionary zeal. The stress, particularly in Part I, is on the use of enzymes for asymmetric syntheses, while biotransformations by microorganisms, surveyed in the latest books, are treated only briefly.

The first chapter in Part I is aimed at familiarizing chemists with the utilization of biochemical systems. Many readers will profit from the section on the specificities of enzyme reactions.

Chapters 2 and 3 (59 and 38 pages, respectively) describe the use of microorganisms and survey the possible reaction types.

Chapter 4, with 394 pages the longest in the book, deals with asymmetric syntheses and enzymatic resolution of racemates. The authors describe in particular proteases oxidoreductases (especially the various alcohol dehydrogenases). There is extensive tabulated material relating to substrate specificity and stereospecificity, collected from widely scattered sources. Much space is devoted to the preparation of compounds that are made chiral by stereospecific isotope substitution. The authors also discuss in detail the application of biochemical methods to the determination of configurations.

Part II is less uniform than Part I. Most of the chapters are less instructive for practical work, but the book makes stimulating reading. *Rose* and *Hanson* give an excellent 45-page account of the stereochemistry of enzyme reactions from the mechanistic and evolutionary points of view, this being an extended version of an article published in 1975 in Accounts of Chemical Research.

A. I. Scott gives a 63-page treatment of biogenetic reaction types, and particularly oligomerization and cyclization with the incorporation of C—C double bonds, as well as rearrangements.

Guthrie devotes a long chapter (103 pages) to numerous aspects of catalysis, and deals with enzyme models and related subjects. In a 60-page account, *Cram* first discusses the bonds in complex formation and then mainly his work on host-guest chemistry, where he mentions many previously unpublished results as well. *Hamilton* describes enzymatic redox reactions and their models in the hope that these enzymes will gain application as reagents in organic chemistry. The last five chapters are again devoted mainly to practical aspects, such as the use of cell-free enzyme systems for organic syntheses on a large scale, affinity chromatography, immobilized enzymes, syntheses with reagents on solid carriers, and enzymatic syntheses of compounds labeled with isotopes other than ^{2}H or ^{3}H.

In all, there are more than 2600 references to research papers and review articles. Each volume has a subject index for Parts I and II. The two Parts are independent, but the distribution of the material between them is somewhat unclear. For the specialist this work brings together many facts and ideas; for the newcomer it can be an excellent catalyst for using biological systems in preparative organic chemistry.

Helmut Simon [NB 405 IE]

Molecular Symmetry and Group Theory. By *A. Vincent*. John Wiley and Sons, London–New York 1977. 1st Edit., ix, 156 pp., bound, £ 5.90.

The author first describes the symmetry elements and symmetry groups, and then deals in the next chapters with the representation of these groups by matrices, determination of the characters of a representation, and resolution of a reducible representation into irreducible ones. He then demonstrates how group theory can give valuable information about chemical bonds and molecular vibrations. All this is presented by the method of programmed learning, *i.e.* in small steps, each followed by a progress-test question and the correspond-

ing answer. If the reader does not give the right answer, he is told which part of the book he should consult again. In some cases no mathematical proof is offered, but the author does state expressly that he finds it more important for the reader to use the mathematical method correctly than to be able to prove all the theories.

The book is a really successful attempt at presenting the scientist with this important and relevant mathematical subject in the most rational manner possible, in such a way that the methods can be used correctly for the solution of problems. It is therefore highly recommended to everyone interested in molecular structure.

H. G. Zachmann [NB 406 IE]

Iminium Salts in Organic Chemistry. Part 1. Edited by *H. Böhme* and *H. G. Viehe*. Vol. 9 in the series Advances in Organic Chemistry, Methods and Results. John Wiley and Sons, New York-London, 1976. 1st Edit., xi, 631 pp., bound, $ 32.00.

In the first chapter, entitled "The Electronic Structure of Iminium Ions" (21 pages), *P. A. Kollman* gives the results of quantum-mechanical calculations on the electronic structure, geometry, rotation barriers, and spectroscopic properties of these ions. In the second chapter, "Structure Determination of Iminium Salts by Physical Methods" (82 pages), *R. Merényi* discusses experimental results given in tabulated form and examines possible equilibria of the type:

$$R_2N{-}CR'_2{-}X \rightleftharpoons [R_2N{=}CR'_2]^{\oplus}X^{\ominus}$$

H. Böhme and *M. Haake*'s third chapter, "Methyleniminium Salts" (117 pages), is fundamental from the preparative point of view. The authors concentrate on the dissociated "*N*-chloromethylamines", and their full account of the methods of preparation will impress even the expert, with its brief description of the physical properties and comprehensive treatment of the reactions.

In the fourth chapter, "The Vilsmeier-Haack-Arnold Acylations. C—C Bond-Forming Reactions of Chloromethyleniminium Ions" (117 pages), by *C. Jutz*, the emphasis is placed on the reactions between dissociated "dichloromethylamines" (derived from amides) and aliphatic compounds. They go beyond the Vilsmeier-Haack formylation, since they give not only aldehydes but also many other products. In Chapter 5, "Chemistry of Dichloromethyleniminium Salts (Phosgeniminium Salts)" (77 pages), *Z. Janousek* and *H. G. Viehe* discuss the dissociated "trichloromethylamines", which are in the same oxidation state as carbamic acid and whose study did not start until 1970. The three replaceable chlorine atoms and the ease of chlorination and aminomethylation open up very wide synthetic possibilities.

The sixth chapter, "α-Haloenamines and Keteniminium Salts" (112 pages), by *L. Ghosez* and *J. Marchand-Brynaert*, deals with covalent α-chloroenamines, which very readily dissociate into ketenimmonium chlorides. Their chemistry is characterized by nucleophilic substitutions of the chlorine atom (aminoalkylenation), enamine-type reactions, and cycloadditions. Chapter 7, "*N*-Heteroiminium Salts" (54 pages), by *J. Elguero* and *C. Marzin*, is devoted to immonium salts with heteroatoms (O, S, N) attached to the nitrogen, examples being derivatives of hydrazines, hydroxylamine, and sulfenic acid amides.

This outstanding book is the first to give such a comprehensive and authoritative account of immonium salts. However, in places one would welcome a more elegant use of formulas and a word or two about the contents of Part 2.

Günter Opitz [NB 398 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Fundamentals of Chemical Relaxation. By *H. Strehlow* and *W. Knoche*. Vol. 10 of the series "Monographs in Modern Chemistry". Edited by *H. F. Ebel*. Verlag Chemie, Weinheim 1977. x, 133 pp., bound, DM 68.—.—ISBN 3-527-25722-5

Das Arbeiten mit ionenselektiven Elektroden. By *K. Cammann*. Vol. 13 of the series "Anleitungen für die chemische Laboratoriumspraxis". Edited by *F. L. Boschke, V. A. Fassel, W. Fresenius, J. F. K. Huber, E. Pungor, W. Simon*, and *T. S. West*. Springer-Verlag, Berlin 1977. 2nd, revised and enlarged edition, xii, 227 pp., bound, DM 76.—.—ISBN 3-540-07947-5

The Use of Chemical Abstracts: A Descriptive Guide to the Organisation. Development and Use of Chemical Abstracts and its Associated Indexes. By *M. B. M. Campbell*. Griffith University Library, Nathan, Queensland 1977. vi, 37 pp., paperback, $ 3.50.—ISBN 0-86857

ESR Spectroscopy in Polymer Research. By *R. Rånby* and *J. F. Rabek*. Vol. 1 of the series "Polymers—Properties and Applications". Edited by *H.-J. Cantow, H. J. Harwood, J. P. Kennedy, J. Meissner, S. Okamura, G. Olivé*, and *S. Olivé*. Springer-Verlag, Berlin 1977. xiv, 410 pp., bound, DM 112.—.—ISBN 3-540-08151-8

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Quantitative Mass Spectrometry in Biochemistry and Medicine

By W. D. Lehmann and H.-R. Schulten[*]

The current state of quantitative analysis with the mass spectrometer in biochemistry and medicine is reviewed. The basic principles of mass spectrometry, the latter's combination with chromatography, the development of sensitive, exact, and in particular specific mass-spectrometric methods of detection, and the principle of dilution with stable isotopes are illustrated by examples. The most important fields of application are: the pharmacokinetics of drugs and active metabolites, investigation of metabolic pathways, supporting of medical diagnoses and enhancement of their specificity, and finally checking the quality of simpler quantitative processes in clinical chemistry.

1. Introduction

This article is concerned with methods of mass spectrometry (MS) and their applications to quantitative analysis in biochemistry and medicine. The measurement processes and their results are presented with the aid of instructive examples and discussed. References to literature containing further information give a survey of the most important investigations of the last 10 years without being complete in the strict sense.

Basically, the advantage of the mass spectrometer as a detection system in qualitative and quantitative investigations is that a high sensitivity is achieved, combined with a high specificity. The quantitative mass-spectrometric determination is always based on the identification of compounds. In complex mixtures, such as occur for example in biological samples, mass-spectrometric analysis is still preceded by a purification and separation process. In this way, a reliable quantitative determination of amounts of material in the microgram to picogram range is achieved.

Many publications have appeared on the possibilities of the most widely used combinations of gas chromatography (GC) and MS (see, for example[1–17]). The most recent results of research into the metabolism of drugs[18–21], the biochemical and medical applications of stable isotopes[22, 23, 273], and quantitative mass spectrometry[24, 286] have been published in a series of conference reports. These relatively new methods have exerted a pronounced influence on drug research in the last few years[25–32]. In the sector of clinical chemistry[33–45] the investigations are centered on the qualitative and semi-quantitative detection of anomalous metabolic products (see Section 7.4). Quantitative measurements, such as precision isotope analysis of the respired air, likewise provide diagnostically valuable information (cf. Section 8.1). Since in biochemistry and medicine there is very often an interest in substances present in very low concentrations together with many other compounds, and moreover the amount of sample available is usually small, the advantages of the mass-spectrometric method of detection are particularly impressive in this field.

2. Basic Principles of Quantitative Mass Spectrometry

The performance of quantitative analyses with the mass spectrometer sets particular demands on the measurement principle. The signal intensity depends not only on the amount of the sample but also on a number of experimental parameters such as the ionization yield, focusing of the ion beam, the transmission of the apparatus, and the amplification factor of the detector. Since it is difficult to determine all these magnitudes individually and to keep them constant over a relatively

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long period, in practice use is always made of a comparative measurement of ion currents. This comparison of the intensities of the signals of the test substance (unknown concentration) and a standard (known concentration) can be performed in several ways:

1) In the first place, a calibration curve of the signal intensities (signal heights or areas) is drawn up as a function of the amount of substance and the unknown concentration is determined from the intensity of the signal by means of this standard curve. Here quantitative determination requires a comparison of two separate measurement processes, calibrated solutions of known concentration being used as an *external* standard.

The added-standard method may also be used. After the sample has been divided into two equal parts, a known amount of the compound to be determined quantitatively is added to one of them. The signal intensities of the untreated sample and of the sample with the added standard are then compared. Since the two parts of the sample must be processed and analyzed separately, this process is included among those with an external standard.

2) If a reference substance in known amount is added directly to the sample to be analyzed and is worked up and analyzed together with the substance of the sample, the process is said to be based on an *internal* standard. If one common type of ion is used for detecting the sample and standard (single ion monitoring), the sample and the standard must be fed into the ion source in succession. This can be done, for example, by separation in a gas chromatograph. With the simultaneous or overlapping introduction of the sample and standard into the ion source, separate recording can be performed, *e.g.* by the detection of selected types of ions (selected ion monitoring, multiple ion monitoring).

Compounds labeled with stable isotopes are in general very suitable as internal standards, since they are clearly distinguishable mass-spectrometrically from the unlabeled compound but are chemically practically identical with it. Homologs or even only chemically similar compounds may also serve as internal standards. In all cases before quantitative analysis the suitability of the selected internal standard should be checked by means of a calibration curve (see Section 4.2).

Before the description of some early investigations, those areas will be introduced whose development is closely related to the advances in the field of quantitative mass-spectrometric analysis.

2.1. Improvement of Microanalytical Separation Processes and Their Coupling or Combination with Mass Spectrometry

For a quantitative determination, the compound concerned must be introduced into the mass spectrometer in the purest possible form (apart from any internal standard used). The gas chromatograph is the separating system most frequently combined with the mass spectrometer. After *Henneberg*'s first experiments[46] with direct coupling of the two instruments, *Ryhage*[47] and *Watson* and *Biemann*[48] developed efficient coupling units (separators) which, on the one hand, reduce the pressure at the outlet of the gas chromatograph to the low value in the ion source of the mass spectrometer and, on the other hand, enrich the sample relative to the carrier gas. Chemical compounds whose thermal lability or low volatility do not permit a gas-chromatographic separation, and which cannot be converted into derivatives[49] with good gas-chromatographic properties, may be worked up before mass-spectrometric analysis *e.g.* by thin-layer, column, or high-pressure liquid chromatography (HPLC)[50]. The application of such a process yields, in addition to purification, additional analytical information (retention time, R_f value) which can be used to confirm the quantitative analysis[51].

2.2. Development of Mass-Spectrometric Recording Techniques for Quantitative Analysis

Several techniques have been developed and tested for measuring the intensities of several ion signals during a time that is limited by the size of the sample:

Repeated passage through a preselected mass range (repetitive scan) by varying the magnetic field strength or the accelerating voltage.

Detecting of selected ions which are focused on the detector in turns and in rapid sequence by variation of the accelerating voltage (selected ion monitoring). The use of GC-MS coupling with this type of ion detection is often called mass fragmentography.

Detection of only one ionic species (single ion monitoring). When an internal standard is used, this type of detection requires that at least two compounds are introduced into the ion source in succession, for example by gas-chromatographic separation.

Use of a multiple detector. Here usually two ionic species are recorded simultaneously under constant instrumental conditions.

The detection sensitivity of these processes for an ion signal rises to the degree in which the proportion of the measuring time of the signal in the total measuring time is increased. Both in the detection of only one ionic species and in the use of a multiple detector an optimum detection sensitivity is achieved, since here this proportion amounts to 100%.

2.3. Availability of Compounds Labeled with Stable Isotopes

In recent years biochemicals labeled with stable isotopes have become commercially available because of the enrichment of the stable isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, *etc.*, carried out on a large scale in the United States[52]. Such compounds have proved to be outstanding as internal standards for quantitative MS investigations. The increasing demand in the last few years has led to a fall in the price of these compounds; thus, 1 g of [D_1]-glucose now costs about DM 400 and 1 g of [1-^{13}C]-glucose about DM 3000. Since microgram amounts of the standard at the most are needed for one quantitative determination, these costs amount to only pfennigs per analysis.

2.4. Coupling of Mass Spectrometer to a Computer

The time required for the recording and processing of the results in mass-spectrometric analyses is considerably reduced by coupling the mass spectrometer to a computer. This permits the treatment of a larger number of samples and creates the prerequisites for routine analysis, *e.g.* in the clinical field.

The recent development of also using the computer for the control and monitoring of the analytical parameters leads to a simplified and better-reproducible operation of the mass spectrometer. Against these advantages there are two disadvantages: on the one hand, the costs of a computer system are of the same order of magnitude as those of a mass spectrometer, and secondly, the complexity of the analytical system and therefore also its susceptibility to breakdown is increased.

3. Early Mass-Spectrometric Investigations with the Detection of Selected Ions on Biochemically Important Compounds

3.1. Specific Recording of the Components in Mixtures

In magnetic mass spectrometers a mass spectrum is usually produced by varying the magnetic field strength. However, it is also possible to focus ions of different masses on the detector by changing the accelerating voltage at a constant magnetic field. Since a voltage can be switched between preselected values considerably faster and more reproducibly than a magnetic field (because of magnet inertia and hysteresis), in magnetic mass spectrometers the accelerating voltage is varied preferentially in order to detect selected ions.

The repeated stepwise variation of the accelerating voltage was used by *Nier et al.*[53] as early as 1948 for the continuous mass-spectrometric monitoring of mixtures of inorganic gases. This type of detection was first used for recording biochemically interesting compounds in 1966, by *Sweeley et al.*[54]. The authors constructed an attachment for the mass spectrometer which permitted the accelerating voltage to jump back and forth between two adjustable values and therefore made possible an almost simultaneous recording of two ionic species of different mass. The aim of this procedure was separate recording of compounds whose mixture could be separated by gas chromatography only partially or not at all. The authors achieved this by the mass-spectrometric detection of selected pairs of ions in the eluate of the gas chromatograph. One of the mixtures investigated is shown in Figure 1.

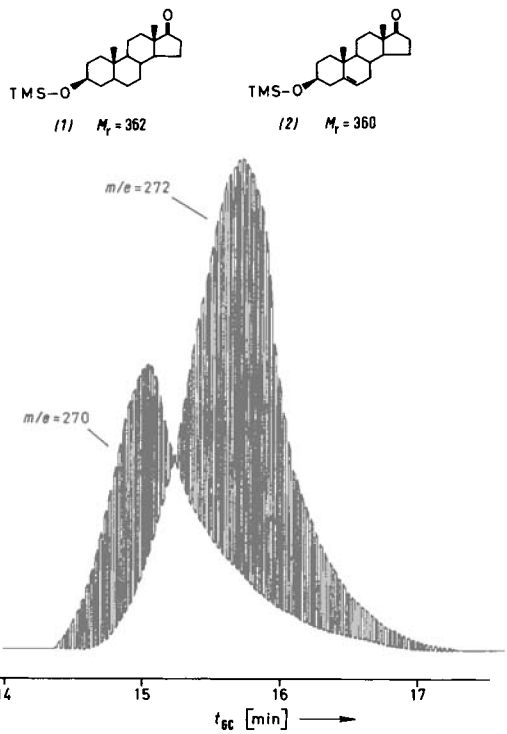


Fig. 1. Separate recording of the trimethylsilyl (TMS) derivatives of epiandrosterone *(1)* and dehydroepiandrosterone *(2)* by recording two selected ionic species (m/e = 272 and 270) with GC-MS. The two substances were partly separated by gas chromatography (t_{GC} = elution time). The mass spectrometer was adjusted in such a way that first with full accelerating voltage the ion with the smaller mass was focused on the detector by variation of the magnetic field. The accelerating voltage was then reduced to such an extent that the heavier ion encountered the detector. During the analysis the accelerating voltage jumped back and forth between the normal value and the adjusted lower value. The line joining the corresponding signal maxima gives two ion-current profiles which permit separate detection of the two compounds (after [54]).

In the same way, in mixtures of glucose and [D_7]-glucose *Sweeley et al.*[54] determined the proportion of the deuterated compound in microgram samples with an accuracy of about 5 %.

In the following years several improved units for varying the accelerating voltage were described[55–65].

In the case of the quadrupole mass spectrometers frequently used today[66] selected kinds of ions are detected by varying the quadrupole field, *i. e.* likewise only by changing electric fields (see also Section 5.3 and 6.2).

3.2. Qualitative Detection of a Drug and its Metabolites

In the first applications of the detection of selected ionic species, *Hammar et al.*[67] identified the drug chlorpromazine and three of its metabolites in human blood with a GC-MS combination. Although two of these metabolites were present in such low concentrations that no complete mass spectrum could be recorded, they could be identified by the fact that the ion-current profiles of three selected ions showed the same intensity ratio as in the mass spectra of the synthetic reference substances and that the retention times of the sample and the reference substance were also in agreement. Obviously with regard to the possibility of being able to identify compounds by the relative intensities of mass-spectrometric *fragments*, the authors called this technique mass fragmentography. In the original literature about 15 terms are found for this technique[68, 69], those most frequently used being mass fragmentography and selected ion monitoring. Here we shall use the terms single ion monitoring and selected ion monitoring, and shall call the results of the measurements selected ion-current profiles.

3.3. Isotopic Dilution and Quantitative Determination

When nanogram amounts are injected into a packed GC column frequently no signal can be obtained at the outlet because of self-absorption and thermal losses. If, however, a form of the compound labeled with stable isotopes is simultaneously injected in a large excess, the absorption capacity of the column acts on the total amount of labeled and unlabeled forms and thus considerably reduces the loss of the unlabeled form. The use of isotope-labeled analogs as carriers in a GC-MS combination permits the detection of compounds in the picogram range[17]. According to recent investigations this frequently described carrier effect does not seem to be a general phenomenon[280].

In a methodological investigation, *Samuelsson et al.*[70] used the addition of a compound labeled with a stable isotope (stable isotope dilution) to increase the sensitivity of a GC-MS combination and simultaneously to perform a *quantitative* detection. They added a trideuterated prostaglandin in approximately 1000-fold excess to a sample containing the undeuterated form and recorded the ion-current profile of the corresponding ions with $m/e = 470$ and 473. A prerequisite for a quantitative determination performed in this way is that the labeled compound added in large excess contains only a very small amount of unlabeled component. In the investigation cited, the proportion of the $[D_0]$ compound in the $[D_3]$-prostaglandin amounted to 0.39%; when this was taken into account, it was possible to determine quantitatively the $[D_0]$ component present in the sample. The limit of detection was about 3 ng, *i.e.* a mixture of 3 μg of the $[D_3]$ component and 3 ng of the unlabeled compound was injected into the gas chromatograph.

The handling of very small samples is facilitated by the use of capillary columns instead of packed columns in GC-MS. In quantitative investigations with amounts of substance with which absorption in the separating system plays a subordinate role, an approximately equimolar ratio between the sample and the standard is selected, since this gives a higher accuracy.

The first quantitative determination of a steroid hormone, *i.e.* an *endogenous* compound, by the detection of selected ionic species was performed by *Siekmann et al.*[71]. By using dideuterated estrone as an internal standard, it was possible to determine the estrone concentration in pregnancy plasma down to 200 ng/2.5 ml. This investigation also showed the high specificity and the high detection sensitivity of this technique (between 1 ng and 50 pg for the steroid hormone investigated).

A little later, *Gaffney et al.*[72] tested a quantitative determination of nortriptyline, *i.e.* an *exogenous* compound, by the same method. This drug is used in the treatment of mental disorders. As the internal standard the authors used both dideuterated nortriptyline and a sulfur "homolog" of this compound. After extraction from blood samples and conversion of the secondary amines to trifluoroacetyl (TFA) derivatives, the compounds were each detected by means of a selected ion after GC separation (see Fig. 2).

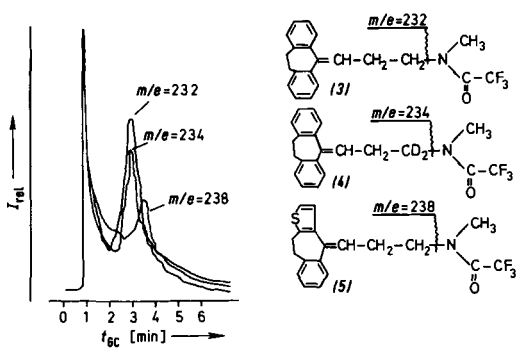


Fig. 2. Analysis of plasma extract containing nortriptyline, $[D_2]$-nortriptyline, and a sulfur "homolog" of this compound in the form of the trifluoroacetyl (TFA) derivatives *(3)*, *(4)*, and *(5)* respectively in the ratio of 1:1:1 (t_{GC} = elution time). The detection of the selected ions with $m/e = 232$, 234, and 238 shows that deuterated and undeuterated nortriptylene are eluted after the same retention time and are recorded with the same sensitivity, while the sulfur-containing compound is eluted later and gives a smaller signal. In quantitative determination in blood plasma it was found that the deuterated compound is more suitable as an internal standard, since at its selected mass there is a smaller superimposition of accompanying substances (after [72]).

In these early investigations quantitative determination was by no means the center of interest. However, on this basis a large number of quantitative mass-spectrometric investigations with a biochemical-medical orientation have been developed.

4. Prerequisites for Quantitative Microanalysis

4.1. Workup and Internal Standard

Although the workup procedure in each determination process must be adapted to the particular sample and the compounds to be detected, certain common features can be described.

A measured amount of the internal standard is added to the sample, *e.g.* a body fluid or homogenized tissue, immediately after it has been collected, and is uniformly distributed in the sample. If part of the compound to be detected is not present in the free form but *e.g.* as a conjugate with glucuronic acid, sulfuric acid, *etc.*, or is bound to a protein (which is frequently the case with drugs), hydrolysis is then carried out to cleave these conjugates (*e.g.* with strong acids or alkalis or enzymatically). If no conjugate is present, or if only the free fraction of the compound is to be determined, the sample is extracted without this step. The extraction is usually carried out by shaking with an organic solvent, which forms a separate phase from the aqueous sample solution[73-75], or by a combination of chromatography and extraction. After the concentration of this extract by removing the solvent under a stream of an inert gas, the mixture of substances must be separated in a special step unless the substance to be detected is already present at such a high concentration that a direct mass-spectrometric analysis can be performed. Suitable methods of separation are gas chromatography, thin-layer chromatography, and high-pressure liquid chromatography, but before GC separation in general the compounds to be detected in the extract must be converted into derivatives in order to increase their volatility and thermal stability. After separation, the sample substance is introduced into the mass spectrometer and is analyzed quantitatively, *e.g.* by the detection of selected ions (see Fig. 3).

In practice a number of purification steps is frequently necessary[38]. Consequently, for quantitative determination the use of an internal standard is the method of choice. A suitable internal standard must on the one hand be as similar as possible to the compound to be determined, so that the concentration ratio adjusted immediately after the sample collection is not changed by workup but, on the other hand, it must be clearly distinguishable mass-spectrometrically from the sample substance. Without an internal standard the yields of each individual extraction and conversion step would have to be determined, while with the use of this standard a single measurement of the concentration ratio of the sample substance and the internal standard is sufficient. The usefulness of an internal standard and of the analytical process can be checked by investigation of calibration mixtures.

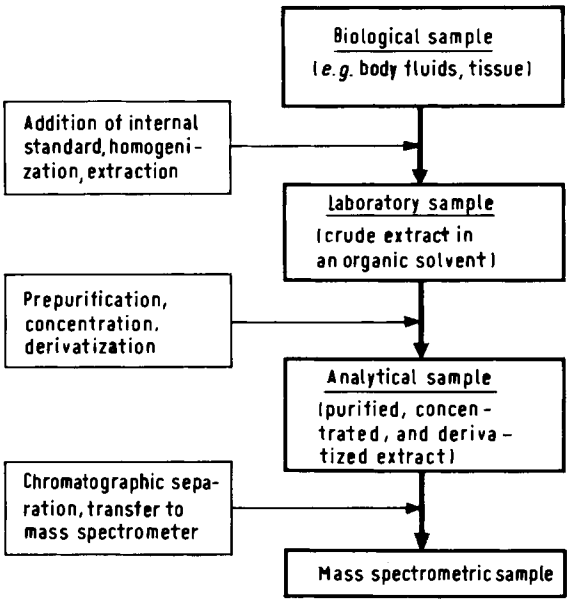


Fig. 3. Schematic process for workup of biological samples for quantitative mass-spectrometric analysis.

fluid (CSF). 5-HIAA is an important degradation product of 5-hydroxytryptamine, a biogenic amine involved in the mechanism of signal transmission in the nervous system.

The course of the calibration curve in Figure 4 shows that $[D_2]$-5-HIAA is a good internal standard. In the investigation of five samples amounts of 8—32 ng of 5-HIAA/ml CSF were found. The mean error of the means determined from 5 measurements in each case was 6 % at 20 ng and 1—2 % for larger amounts.

Figure 5 shows a different position of the calibration curve in connection with the detection of an ionic species and the use of a compound of similar structure as an internal standard. *Walle et al.*[78] determined the amount of the drug propanolol and its active metabolite 4-hydroxypropanolol in human blood plasma. For this purpose they used GC-MS and the detection of a common fragment ion of the drug, metabolite, and standard.

In order to ensure the specificity of the whole detection process and to test the proportionality between the amount of substance and the analytical results, calibration curves should be constructed before the quantitative determinations.

4.2. Calibration Curves

As the basis of quantitative mass-spectrometric determinations, it should be checked on calibration mixtures made up of the sample substance and the standard whether linearity exists between the composition of the mixture and the measured values, *i.e.* the ratio of the signal height or areas in the ion-current profile, in the concentration range of interest. In accordance with the conditions of analysis of authentic samples, these calibration mixtures are usually made up by adding different amounts of the sample substance to a constant amount of internal standard. Fig. 4 shows a calibration curve drawn up by *Bertilsson et al.*[76] by this method. By means of a GC-MS combination and the detection of selected ionic species, these authors determined the concentration of 5-hydroindole-3-acetic acid (5-HIAA) in human cerebrospinal

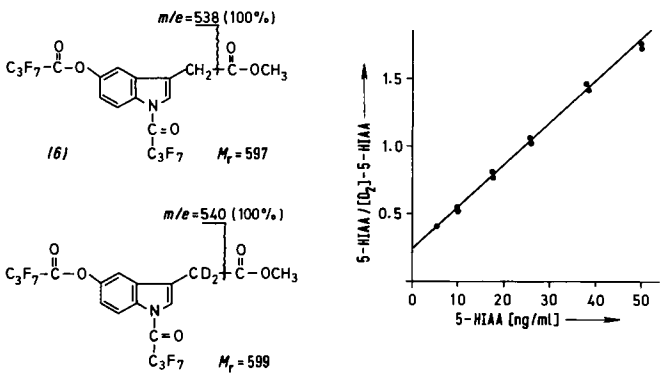


Fig. 4. Calibration plot (based on signal heights) for checking a quantitative assay. Calibration mixtures were prepared and analyzed that contained in each case 40 ng/ml of internal standard ($[D_2]$-5-hydroxyindole-3-acetic acid, $[D_2]$-5-HIAA) and different amounts of 5-hydroxyindole-3-acetic acid (5-HIAA) in synthetic cerebrospinal fluid (CSF) [77]. The plot shows linearity between the analytical values and the 5-HIAA concentration. The intercept on the ordinate agrees with the assumption that the internal standard contained 20 % of the $[D_0]$ component. For the GC separation it was necessary to make the bis(heptafluorobutyryl) (HFB) methyl ester derivatives *(7)* and *(6)* (after [76]).

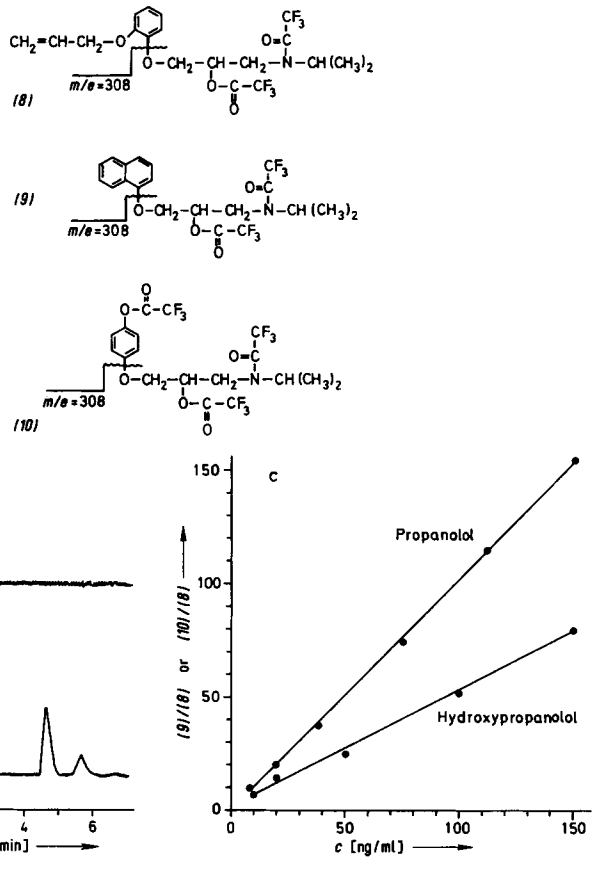


Fig. 5. Calibration plots (based on signal areas) and ion-current profiles for the quantitative determination of propanolol and 4-hydroxypropanolol [in the form of the trifluoroacetyl (TFA) derivatives *(9)* and *(10)* with oxprenolol [in the form of the TFA derivative *(8)*] as internal standard. A) Blank value of the ion current at $m/e = 308$ in the analysis of plasma without the administration of propanolol and without the addition of the internal standard; B) after the administration of propanolol and addition of *(8)*; C) the calibration plots pass through the origin, since no other ions with $m/e = 308$ interfere. The slope of *ca.* 1 in the plot for propanolol shows that the sensitivities for components *(8)* and *(9)* are practically the same. The slope of the calibration curve of *(10)* is only about half as large, which indicates loss of the substance during working up and separation (after [78]).

In general, the calibration curves are plotted from the measurements by the method of least squares. The use of compounds labeled with stable isotopes as internal standards almost invariably gives plots with a slope of unity (within the accuracy of the measurements), passing through the coordinate origin if the standard contains practically no unlabeled component and there is no superimposition of impurity ions. When compounds labeled with ^{13}C, ^{18}O, ^{15}N, *etc.*, (but not deuterium-labeled compounds) are used and the work is carried out at relatively high concentrations (>10 ng/ml), under certain conditions calibration curves need not be constructed[28]. Such compounds show optimal chemical similarity to the unlabeled analog to be determined. No disturbances due to replacement of the labeled by unlabeled atoms or to isotope effects are to be expected.

5. Comparison of Mass-Spectrometric Techniques for Quantitative Determinations

5.1. Accuracy, Precision, and Sensitivity

The *accuracy* of a measurement represents its deviation from the true value. Systematic errors always affect measurements in one direction and therefore affect accuracy, while fluctuations arising statistically average out with increasing number of measurements.

The *precision* gives a measure of the reproducibility of the measurements when the same sample is analyzed repeatedly. The precision is expressed as the relative or absolute standard deviation of the arithmetic mean of a set of measurements[79].

The *sensitivity* of a measurement is described by the ratio of the recorded magnitude of the signal to the amount of sample used. In mass spectrometry it is given, for example, as coulomb/μg.

In what follows the mass-spectrometric detection techniques used for quantitative analysis will be described in the sequence of increasing precision and sensitivity.

5.2. Repetitive Scanning of a Preselected Mass Range

Comparative measurements of the intensity of several ionic species can be carried out without additional apparatus by repetitive scanning of a preselected mass range (repetitive scan) (see, for example[80]). With relatively large amounts of the sample, at a constant total ion current, the signal intensities can be compared directly (see Sections 6.3 and 10.3). If, because of the small sample size or because of the nature of the sample introduction (*e.g.* by direct GC coupling), the total ion current cannot be kept constant over the period of a few mass scans, after the measurement the ion-current profiles of individual types of ions can be reconstructed from the recorded mass spectra. This can be done effectively only when the results are fed into and processed by a computer (see Section 6.2). In this case the areas of the ion-current profile are usually used for the comparative measurements.

The scanning of a mass range yields less accurate values than the processes described below[81,82], since a large part of the measurement time is not used for recording the ions of interest. In addition to this, there is the fact that to record undistorted mass spectra certain adjustments of the resolving power and the time constant of the amplification system must be maintained that do not permit an adjustment to the optimum sensitivity. These disadvantages can, however, be partially compensated if only a small section of the mass spectrum is scanned and a multichannel analyzer is used for accumulation of the signals[268,271].

5.3. Detection of Selected Ions

The precision of the determination of the intensity of selected ions with a magnetic mass spectrometer depends on the stability of the magnetic field, the accelerating voltage, and the amplification system, and also on the amount of the sample. In the nanogram range the precision is of the order of 1–2 % if approximately equal amounts of the sample and the standard compound are present. In the case of amounts of substance in the microgram range the precision increases, whereas in the subnanogram range a precision of only about ±10 % is obtained. The decrease in precision with smaller amounts used for analysis is due to the increase in the statistical fluctuations of the ion current and the difficulties in reproducible handling of very small samples. The best values reported are a precision of about ±0.3 % for an amount of 3 ng and ±10 % for 30 pg[83]. These figures were obtained with a combination of a capillary-column GC and MS.

Comparable precisions have been found on working with a quadrupole mass spectrometer[84]. As compared with magnetic instruments, this has the advantage that the times for the jumps between the preselected masses are still shorter and that ions of any desired mass can be selected (in the case of the magnetic instrument the smallest selected mass must amount to at least some 60 % of the highest mass). On the other hand, in the quadrupole apparatus when the masses are far apart a correction must be made for the mass dependence of the ion transmission.

The main sources of error in quantitative determinations lie in adsorption-desorption effects in the separating system or in the glassware used and, especially, in the comparatively simple metering of the internal standard. In the preparation of the standard solutions and in the measuring out of an aliquot—typical amount 20 μl—to be added to the sample, errors amounting to a few percent may quite easily arise. This applies above all to the case in which a relatively large number of samples is processed and routine measurements, *e.g.* in the clinical field, are performed over a relatively long time.

5.4. Detection of Only One Type of Ion (Single Ion Monitoring)

Referred to the analysis of the same amounts of substance, in the detection of only one type of ion a greater precision is always achieved than in the detection of several selected ions, since in the first case 100 % of the measurement time is utilized for recording. In a comparative study on the quantitative analysis of a barbiturate by these two methods, *Lee* and *Millard*[85] showed that the increased precision has an effect only in the region of amounts of substance smaller than 1 ng. In the subnanogram range the authors achieved the greatest precision by adding to the sample a related barbi-

turate as an internal standard and a deuterated derivative in excess as a carrier for the GC separation, and performed the quantitative determination by detecting a common fragment ion of the sample and standard.

5.5. Simultaneous Detection with a Multiple Detector

Precision isotope determinations can also be carried out with a precision of up to $1:10^5$ by means of special mass spectrometers. For this purpose, however, large amounts of sample, comparison with a standard mixture of accurately known isotope distribution, and recording with a multiple detector are necessary. Multiple detectors usually record two types of ions simultaneously, and because of their construction they are limited to a relatively low range of masses. They are particularly suitable for gas analysis, *e.g.* for the precision measurement of the amount of ^{13}C or ^{18}O in CO_2, where the ions of masses 44 and 45 or (44+45) and 46 are collected simultaneously (see Section 8.1).

6. Examples of Application: Quantitative Determination of Drugs

6.1. GC-(EI)MS Coupling—Determination of the Steady-State Blood Level of Imipramine and Desipramine

The tricyclic compound imipramine *(11)* is frequently used for the chemotherapy of mental disorders. The individual response to this drug differs widely, so that the same daily dose may be therapeutically effective, ineffective, or even toxic.

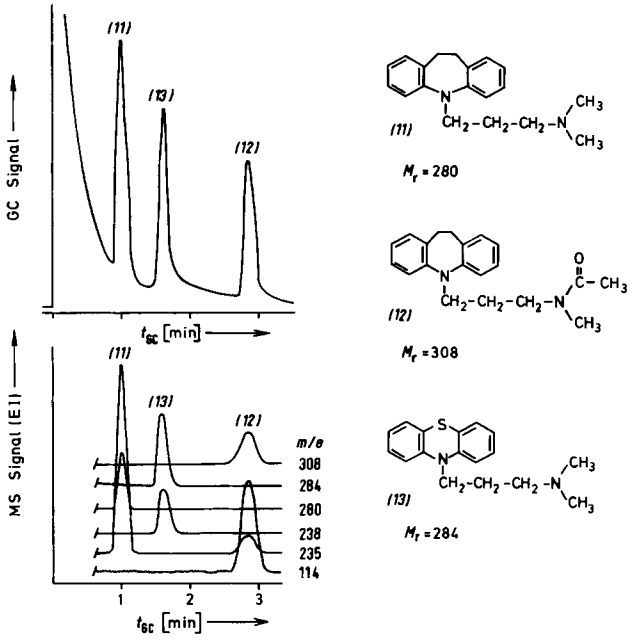


Fig. 6. Gas chromatogram and selected ion-current profiles of an extract from blood plasma after the administration of imipramine *(11)*. For the gas-chromatographic separation the metabolite desipramine was converted into the acetyl derivative *(12)*. On the basis of the EI spectra the following ions were selected for the recording (relative intensities [%] in parentheses): $m/e=280$ (20) and 235 (73) for imipramine *(11)*; $m/e=308$ (30), 235 (10), and 114 (100) for acetyldesipramine *(12)*; $m/e=284$ (17) and 238 (13) for promazine *(13)*. Since the ion-current profiles were recorded with a quadrupole mass spectrometer, it was possible to choose fairly well separated maximum and minimum recorded masses (after [86]).

In the determination of the concentrations of imipramine and its demethylated metabolite desipramine in blood samples of various patients receiving the same daily dose, again large individual variations can be found. For example, *Belvedere et al.*[86], using a combination of a gas chromatograph and an electron impact (EI) mass spectrometer and the detection of selected ionic species, investigated the steady-state plasma concentrations of imipramine *(11)* and desipramine in patients receiving a constant daily dose of imipramine. As the internal standard they used promazine *(13)*, a chemically related compound. The calibration curves showed linearity between the compositions of the mixtures and the analytical results in the range of concentrations of 5—200 ng/ml plasma. Figure 6 shows the elution behavior of the compounds and the form of the selected ion-current profiles.

The sensitivity of the process reaches about 5 ng/ml plasma. In the investigation of one patient it was possible to show that about one week after adjustment to a daily dose of 75 mg of imipramine a constant blood level equal to about 70 ng/ml of imipramine and about 15 ng/ml of desipramine was achieved.

6.2. GC-(CI)MS Coupling—Determination of the Steady-State Blood Level of Imipramine and Desipramine

In an almost simultaneous study, *Claeys et al.*[87] also determined the plasma concentrations of imipramine and desipramine with a constant daily dose. For both compounds the authors synthesized a tetradeuterated internal standard and used chemical ionization (CI)[88,89] with methane as the reaction gas, since in the CI(CH_4) mass spectra the $[M+H]^+$ ions appear with 100% relative intensity. In contrast, the EI mass spectra show only molecular ions of lower intensity. The mode of detection used was fast repetitive scanning of

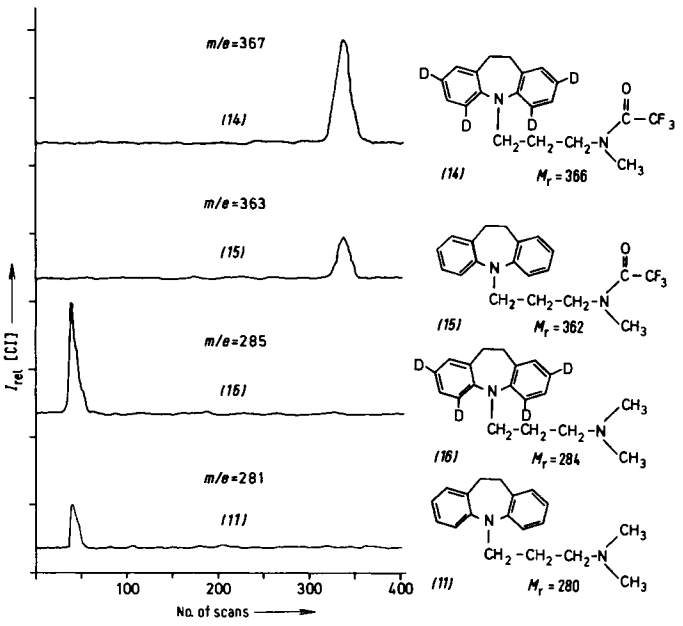


Fig. 7. Reconstructed ion-current profiles of imipramine *(11)*, trifluoroacetylated desipramine *(15)*, and their deuterated derivatives *(16)* and *(14)* as internal standards in the GC-(CI)MS investigation of a plasma sample. The CI quadrupole mass spectrometer was coupled directly to a computer, which recorded the mass spectra in rapid sequence (100 spectra per minute) and then reconstructed the ion-current profiles of the selected signals at $m/e=280$, 284, 362, and 366 from these and displayed them (after [87]).

a preselected mass range and computer reconstruction of the selected ion-current profiles from the stored results. (The ion-current profiles so obtained are frequently called "mass chromatograms"[90, 91].) The investigation was carried out with a quadrupole mass spectrometer coupled directly with a gas chromatograph and a computer. Figure 7 shows an example of the ion-current profile.

Investigation of six patients who had been adjusted to a daily dose of between 250 and 350 mg of imipramine *(11)* gave values between 55 and 290 ng/ml for the constant blood level achieved. The ratio between the drug and the demethylated metabolite desipramine varied between 0.5 and 1.85 in these patients. In this relatively small group of patients no correlation could be determined between the measured concentrations and the therapeutic result. However, in more recent detailed clinical investigations such a relationship has been found[92, 93].

6.3. (EI)MS with Direct-Inlet Systems—Pharmacokinetics of Cyclophosphamide in Single Dose Therapy

Cyclophosphamide *(17)* is one of the most frequently used antitumor drugs[94, 95]. It has been possible to identify some of its metabolites by selected ion monitoring (see for example[95]). Cyclophosphamide is administered in high single doses (between 10 and 100 mg/kg body weight[96]). Because of the resulting high concentrations in the blood and urine, the drug can be determined quantitatively with a mass spectrometer without a preliminary chromatographic separation. *Jarman et al.*[97] investigated the pharmacokinetics of cyclophosphamide *(17)* in blood by adding to the samples the tetradeuterated derivative *(18)* as the internal standard, extracting the plasma samples with dichloromethane, and introducing the evaporated extract into an electron impact (EI) mass spectrometer by the direct inlet system. The results of this investigation are shown in Figure 8.

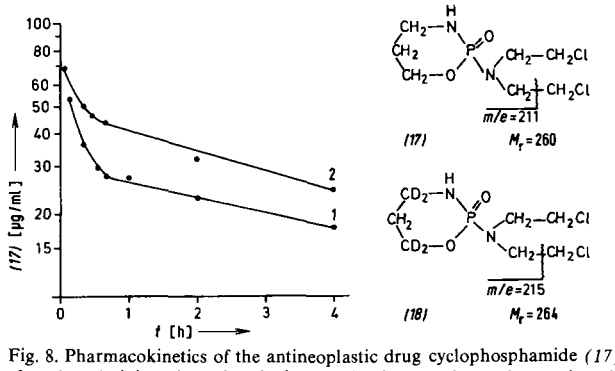


Fig. 8. Pharmacokinetics of the antineoplastic drug cyclophosphamide *(17)* after the administration of a single dose (patient 1, 12.5 mg/kg; patient 2, 27.8 mg/kg). The concentration scale is graduated logarithmically; the half-life of the drug can be calculated from the slope of the linear part of the curve. For the quantitative determination, at constant total ion current, a small mass range containing the fragment ions of masses 211 and 215 of the sample substance *(17)* and of the standard *(18)* was scanned repeatedly (after [97]).

The authors found a precision of 1% at concentrations greater than 10 µg/ml and deviations of 10% at 1 µg/ml. At still lower concentrations the signals of other compounds interfere, so that a purification of the extract would be necessary. This work shows that at relatively high concentrations of a drug the specificity of the mass spectrometer together with the method of dilution with a standard labeled with a stable isotope alone (without previous chromatographic separation) is sufficient for reliable quantitative determination.

6.4. GC-(EI)MS Coupling—Pharmacokinetics of a Single Dose at a Constant Daily Dose

When drugs are used over a long period they frequently accumulate in the tissue in a storage form—for example bound in the tissue (*e.g.* to protein)—and thus maintain a certain blood level for a time after the administration of the drug has been stopped. *Sullivan et al.*[98] succeeded in detecting the different availabilities of permanent doses and a pulse dose of a drug by quantitative mass-spectrometric measurements. For this purpose they gave dogs a daily dose of about 60 mg of the analgesic propoxyphene and on the 20th day replaced this dose by an equal amount of $[D_2]$-propoxyphene. The changes in the concentrations of the two components in plasma samples were then followed as a function of time. They were determined quantitatively by coupled GC-(EI)MS, selected ion monitoring, and the heptadeuterated compound as the internal standard. The calibration plots were linear and showed a high precision of the determination (standard deviation 0.5—2%). The differences between the changes in concentration can be seen in Figure 9.

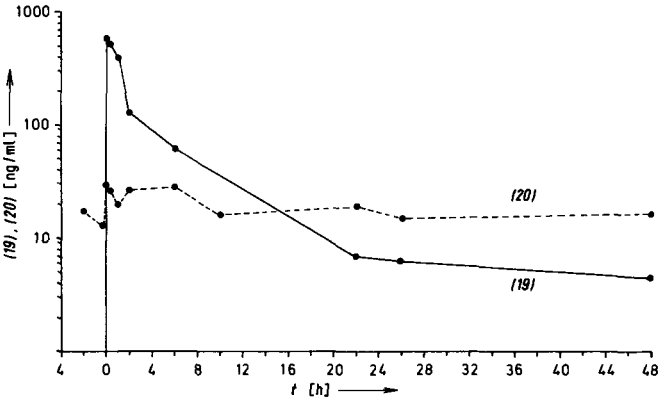


Fig. 9. Pharmacokinetics of a single dose of $[D_2]$-propoxyphene *(19)* (5.5 mg/kg) on day 20 (time 0) in dogs given a constant daily dose of $[D_0]$-propoxyphene *(20)* (also 5.5 mg/kg). After a steep rise of the level of the deuterated drug *(19)*, its concentration fell substantially faster than that of the $[D_0]$ drug *(20)*. This means that there is a relatively large depot of tissue-bound $[D_0]$-propoxyphene *(20)*, from which an almost constant concentration of the $[D_0]$ component is maintained in the blood (after [98]).

The investigation showed that, by labeling with stable isotopes, it is possible to distinguish doses of a drug administered at different times and also to elucidate their specific pharmacokinetics.

6.5. Brief Review of Other Determinations of Drugs

Most quantitative determinations of drugs have been performed with GC-(EI)MS. The use of thin-layer chromatography as a purification technique in combination with mass spectrometry is rarer[99]. Just like (EI)MS, (CI)MS is occasionally used with the direct-inlet system[82, 100–102]. Only the names of other preparations or drugs determined quantitatively will be given here, in alphabetical order: acetani-

lide[103,274], amphetamine[105-107,275], amobarbital[276], amylobarbitone[104], bromisoval metabolites[108], bupivacaine[277], cannabis compounds[109-111], capsaicine[112], diphenylhydantoin[278], ephedrine[114], ethanol[113], guanethidine[115], ketamine[279], lidocaine[102,116], methadone[119], methaqualone[117,118], methylphenidate[120], morphine[121-123], nortriptyline[124], octopamine[280], pentazocine[125], phencyclidine[126,281], phenformin[127], phenylbutazone[282], pinazepam[128], pirbuterol[129], propanetheline[283], propoxyphene[130,131], salbutamol[132], terbutaline[133], trazodone[134], verapramil[284], and vincamine[285]. The aim of such investigations is, for example, the measurement of therapeutically active concentrations, determination of the pharmacokinetics of drugs and their active metabolites, measurement of the rate of excretion, and the determination of the concentration ratio of a parent drug to its metabolites.

By labeling drugs with stable isotopes it is also possible to observe isotope effects in the *in vivo* metabolization (see, for example, [135-137]). For its recognition, after the administration of, for example, a 1:1 mixture of unlabeled and labeled drugs the isotope distribution in the metabolites or the drug itself is followed. Particularly large effects appear if there are several approximately equally justified degradation pathways and in one of them the rate constant is altered by the isotopic labeling (metabolic switching). The isotope effects in *in vivo* metabolization observed hitherto always related to the replacement of hydrogen by deuterium, in which, because of primary isotope effects, the enzymatic degradation of the labeled compound was retarded.

In many cases the described combinations of chromatographic and mass-spectrometric methods give a differentiated and more reliable insight into the course and the kinetics of drug metabolism than has been possible by other methods.

7. Examples of Application: Quantitative Determination of Endogenous Compounds

The advantages described in the preceding section also apply to the determination of endogenous compounds, *i.e.* compounds produced by the body itself, since the same measurement procedure is used for the direct quantitative determination of these compounds. Since many important compounds in body fluids and tissues are present in very small concentrations, and in the collection of samples from patients the available amount of the sample is limited, the use of isotopically labeled carriers is particularly important in such cases.

7.1. GC-(EI)MS Coupling—Determination of an Endogenous Compound in the Urine, Plasma, Cerebrospinal Fluid, and Brain and Liver Tissues

With only slight variations in the extraction and preparation of the samples, *Sjöquist et al.*[138] were able by means of a GC-MS method to measure the concentrations of 4-hydroxy-3-methoxyphenylglycol (HMPG), the most important metabolite of norepinephrine in samples of human and animal origin. The use of the trideuterated compound as an internal standard gave values of good precision (see Figure 10 and Table 1).

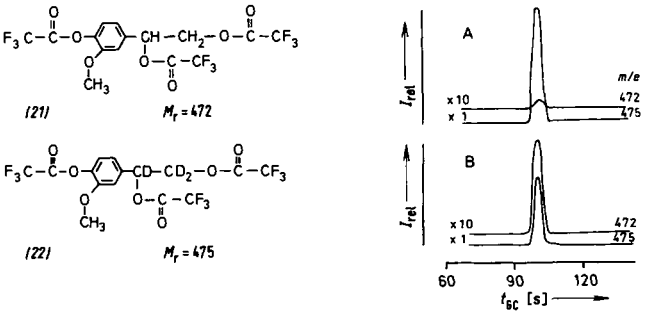


Fig. 10. Example of a quantitative determination of 4-hydroxy-3-methoxyphenylglycol (HMPG) with [D_3]-HMPG as an internal standard; the compounds were analyzed in the form of the tris(trifluoroacetyl) (TFA) derivatives *(21)* and *(22)*. A) Ion-current profiles of $m/e = 472$ and 475 of the internal standard *(22)* to check its contribution to the mass of the undeuterated compound (here 0.8%). B) Ion-current profiles of $m/e = 472$ and 475 in the measurement of a rat brain tissue extract (after [138]).

Table 1. Concentration of 4-hydroxy-3-methoxyphenylglycol (HMPG) in body fluids and tissues (after [138]).

Sample	HMPG [nmol/ml] or [nmol/g]	No. of determinations	Rel. standard deviation [%]
Man			
Plasma	0.056 ± 0.003	18	5.4
Urine	7.4 ± 0.21	20	2.8
Cerebrospinal fluid	0.073 ± 0.006	16	8.2
Rat			
Urine	24 ± 0.86	6	3.6
Brain	0.26 ± 0.016	10	6.2
Liver	0.099 ± 0.013	6	13

According to Table 1, the HMPG concentrations in the individual samples differed considerably. These values apply to the total HMPG concentration, *i.e.* they are sums of free and conjugated forms of the compound; before working up, the samples had been hydrolyzed enzymatically with sulfatase. By subtracting the concentration found without hydrolysis it is possible to determine the proportion of the compound present in conjugated form. In man this amounts to respectively about 94% and 90% in the urine and plasma, while in the cerebrospinal fluid it is 25%.

7.2. Quantitative High-Resolution Mass Spectrometry—Determination of Steroids with the Direct Inlet System and an External Standard

The tissue of human ovaries contains relatively high concentrations of steroid hormones in comparison with other tissues. *Snedden* and *Parker*[139] introduced freeze-dried tissue sections of ovaries *via* the direct-inlet system into an EI mass spectrometer and used a reproducible heating program going up to about 220°C to vaporize the volatile constituents of the sample. They obtained signals for estrone, estradiol, and progesterone, and found that at a mass-spectrometric resolution of 10000 no signals of other compounds interfered. During an evaporation process, by selected ion monitoring they recorded the ion-current profiles of one ion each of the three steroids investigated and one ion of the calibration substance perfluorotributylamine to check the exact mass position. The quantitative determination was performed by comparing the areas of the ion-current profile with the corresponding areas

of calibration measurements performed separately, *i.e. via* an external standard. The amounts of the steroids detected were between 10 and 50 ppm referred to the weight of the dried tissue; the standard deviation was about 20 %, which must be ascribed partly to the external calibration and partly to the fact that no homogenization of the tissue samples was performed. This investigation, and also an earlier one by the same authors[140], shows that in certain cases it is possible to use, in place of a separation, an increase in the mass-spectrometric resolution for specific and also quantitative determinations. In some cases high-resolution mass spectrometry has also been used in a GC-MS coupling for quantitative measurements[141, 142].

7.3. Spark-Ionization Mass Spectrometry—Quantitative Determination of Metals

The determination of inorganic constituents such as metals in biological material is an important analytical task. Spark-ionization mass spectrometry is a very versatile and sensitive method for the detection of metals. Since a photographic plate is used in most cases as the detector, the quantitative detection is more laborious than with electrical recording, but it is also suitable for routine operation[143, 144]. Measurements with internal[145, 146] and external[147] standards have been performed. *Ball et al.*[148] have determined a large number of elements, mostly metals, in the ash of mammalian blood by spark-ionization mass spectrometry and high resolution. For quantitative determinations calibration plots were constructed, correlating the degree of photographic blackening with the amount of sample. Some of the results are shown in Table 2.

Table 2. Metal content of the ash of mammalian blood determined quantitatively by spark-ionization mass spectrometry. 20 other elements are not given here (after [148]).

Element	Concn. [μg/ml] (wet weight)
Na	1930
Mg	59
Al	0.32
K	2250
Ca	44
Cr	0.07
Mn	0.35
Fe	1050

The range of error of the measurements is given as 15 %; this is due partly to calibration with an external standard and partly to the evaluation of the photographic plate, which alone causes errors of between 2 and 5 %. Recently, however, very sensitive determinations of metals in the form of porphyrin chelates by EI-MS were reported, in which multiply-deuterated porphyrin chelates were used as internal standards[149].

In biochemical analysis the isotope dilution technique has also been used for the quantitative determination of calcium[150], lead[151], and potassium[152].

7.4. Recording of Metabolic Profiles

An important question in the quantitative determination of endogenous compounds is that of the diagnostic value of the concentrations measured. Extensive investigations in which many metabolic products were determined simultaneously (metabolic profiling)[37, 75, 153] have shown that the concentrations that have to be regarded as normal values have a relatively wide range of variation. These natural variations are due to individual metabolic and to dietary differences.

Deviations in the metabolic profile of the urine, which frequently go far beyond the normal range of fluctuations, are caused by a number of congenital metabolic disorders[34, 35, 40, 41]. Here, because of some genetic defect, the organism may be unable to synthesize an enzyme, so that a certain substance can no longer be degraded normally in the body; this leads to a considerably increased excretion of this substance or of some unusual degradation products. Figure 11 shows the metabolic disturbance in the well-studied disorder known as phenylketonuria (PKU), which is characterized by the absence of the enzyme needed to convert phenylalanine *(23)* into tyrosine *(24)*. Patients with PKU therefore show extremely high urine concentrations of phenylalanine *(23)*, phenylpyruvic acid *(25)*, and other aromatic carboxylic acids, which are not hydroxylated in position 4. In addition, 4-hydroxyphenylpyruvic acid and 4-hydroxyphenyllactic acid are present in increased concentrations because of secondary enzyme inhibition.

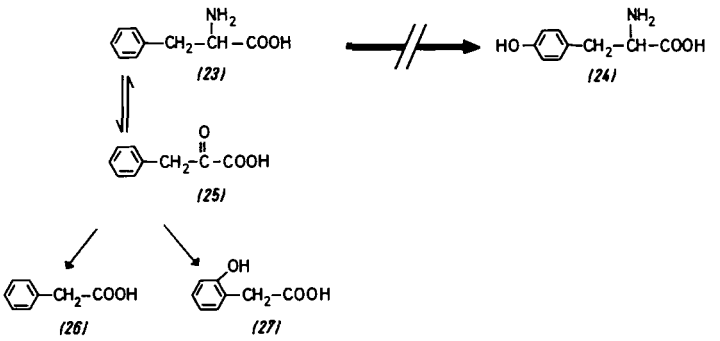


Fig. 11. Scheme of the hereditary metabolic disease phenylketonuria (PKU). The capacity for the synthesis of the enzyme that normally hydroxylates phenylalanine *(23)* to tyrosine *(24)* is lacking (metabolic block) (after [230]).

The recording of metabolic profiles by GC-MS is of particular importance for the early recognition of congenital metabolic defects in newborn babies and children. The occurrence of unusual compounds in high concentrations frequently causes, for example by competitive inhibition of other enzyme systems[154], severe disturbances in physical and mental development. On early recognition, these consequences can be almost completely avoided by a suitable diet—in the case of PKU, for example, by a phenylalanine-poor diet.

Quantitative mass spectrometry plays only a subordinate role in the recognition of congenital metabolic diseases, since the deviations are usually so great that they can be recognized directly from the gas chromatogram and in some cases can be determined quantitatively. Attempts have been made to develop computer-supported GC-MS analyses for diagnosing pathological abnormalities in the metabolic profile, so that even relatively large groups of patients can be investigated in routine analysis[155].

7.5. Determination of Other Endogenous Organic Compounds

The quantitative determination of endogenous compounds occupies an area as wide as that of drugs and their metabolites. Two of the best-investigated classes of compounds are steroids[156-175] and prostaglandins[176-187]. The distribution of biogenic amines[154,188-200], metabolically related compounds[201-211], and quaternary ammonium cations[287-291] in body fluids and tissues has similarly been intensively investigated. Other substances determined quantitatively by mass spectrometry include a number of amino acids[212-216], bile acids[217-219], carboxylic acids excreted in the urine[37,75,220], and a tetrasaccharide[221], which was also found in the urine.

8. Determination of Stable Isotopes in Metabolic Products

8.1. The Respiration Test: Precision Measurement of Carbon-13 Abundance

In the quantitative determinations already mentioned the main attention was directed at the measurement of the concentrations of organic compounds. For this purpose, directly after collection of the sample, by the addition of an internal standard labeled with stable isotopes a certain isotope ratio was generally produced artificially and was analyzed. It is also possible to provide an organism with a compound having a known isotope ratio as a substrate and to follow its degradation by measuring the isotope ratio in a metabolic product. A very promising field of application of this principle is the ^{13}C respiration test, *i.e.* the precise determination of ^{13}C in the CO_2 of expired air after the administration of compounds enriched in ^{13}C. A series of investigations has been performed with ^{14}C-labeling and following of the radioactivity in the expired air. Because of the absence of radiation the use of stable isotopes is also preferred here, particularly since results of informative value are obtained by both techniques. For example, *Shreeve et al.*[222] came to this conclusion in a test of the function of liver microsomes in which the subjects were fed with galactose labeled with both ^{13}C and ^{14}C. A reduced elimination of $^{13}CO_2$ or $^{14}CO_2$ shows a disturbance of microsomal function.

Since in the respiration test an adequate amount of the sample is available, intense ion currents constant over relatively long measurement times can be obtained in the mass-spectrometric analysis. The recording is carried out by means of a double detector which, in the case of the analysis of ^{13}C in CO_2, collects the ions of masses 44 and 45 simultaneously. If the isotopic composition of the sample is determined relative to a standard mixture of accurately known composition, a precision of up to $1:10^5$ can be achieved. Thus, the precision of the method exceeds the natural range of fluctuation of the abundance of ^{13}C in respired air[223,224], which is the factor limiting the sensitivity of the respiration test.

The possibilities of the method may be illustrated on an interesting example of its application due to *Lacroix et al.*[225-227], who performed a respiration test after the administration of *naturally* ^{13}C-labeled glucose. They found a $^{13}C/^{12}C$ ratio of 0.01085 in the CO_2 of the respired air of six subjects who had fasted overnight. In contrast, glucose obtained from maize, after combustion to CO_2, shows a higher ^{13}C abundance, namely 0.01100. For the experiment the subjects were given 100 g of this glucose dissolved in 400 ml of water, and subsequently samples of blood were collected at regular intervals for determining the glucose concentration and samples of respired air for the carbon isotope analysis. The results of these measurements are given in Figure 12.

The precision of the mass-spectrometric isotope analysis of carbon dioxide is so high that relatively small deviations in the isotope ratio of glucose from a natural source can

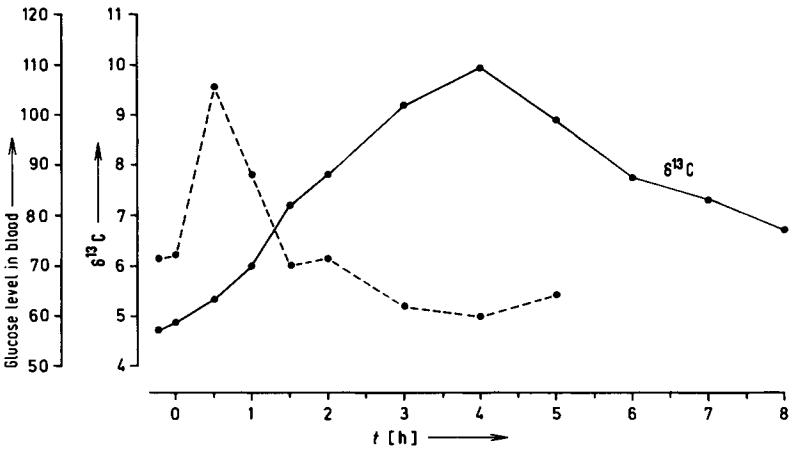


Fig. 12. Time variation of the blood level of glucose (---) and of the $^{13}C/^{12}C$ ratio $\delta^{13}C$ (—) in the expired air after the administration of 100 g of maize glucose (mean values for six subjects with normal glucose metabolism). The ^{13}C abundance is expressed relative to a standard with the ratio $^{13}C/^{12}C = 0.010806$, where

$$\delta^{13}C = 10^3 \left(\frac{(^{13}C/^{12}C)_{sample}}{(^{13}C/^{12}C)_{standard}} - 1 \right)$$

Expressed in these units, the maize glucose used after combustion to CO_2 showed a $\delta^{13}C$ value of 17.9 ± 0.3 (after [225]).

still be determined indirectly through biological degradation. As a result of a special synthetic pathway in plants, glucose obtained from maize and from sugar cane exhibits a higher ^{13}C content than glucose obtained from sugar beets, the ^{13}C abundance of which is only slightly above the mean ^{13}C abundance in the CO_2 of respired air.

Similar diagrams can be drawn up with substantially smaller amounts of glucose highly enriched with ^{13}C. In the case of persons with a disturbed glucose metabolism (*e.g.* diabetes), the glucose concentration curve shows a higher maximum and the ^{13}C curve a considerably flatter shape. Such experiments, in which enzyme activities can be determined indirectly with ^{13}C labeling with no exposure to radiation, are particularly important for the investigations on children and pregnant women.

A ^{13}C analysis of CO_2 through the detection of selected ions was used by *Sano et al.*[228] to determine ^{13}C-labeled compounds in urine samples. For this purpose the authors coupled a gas chromatograph *via* a pyrolyzer to a mass spectrometer, so that the organic samples were analyzed mass-spectrometrically after complete combustion. The $^{13}C/^{12}C$ ratio was given directly as an analog signal, so that the occurrence of a ^{13}C-labeled compound in the GC eluate could be recognized as a peak.

8.2. Investigation of Metabolic Pathways with Stable Isotopes

Stable isotopes find an elegant application in the *in vivo* study of metabolic degradation and synthesis pathways[229]. After loading of an organism with specifically-labeled substrates, the mass-spectrometric analysis of the metabolic products can give their content of labeled atoms; often, by showing the fragmentation, the mass spectrum also provides information on the position of the labeled atoms within the molecule.

Curtius et al.[230] were able to show on patients with PKU (see Fig. 11) that after administering deuterated phenylalanine only metabolites such as phenylpyruvic acid *(25)*, phenylacetic acid *(26)*, and 2-hydroxyphenylacetic acid *(27)* occurred in deuterated form in the urine, while no 4-hydroxylated products contained deuterium. This confirmed the presence of a metabolic block between phenylalanine and tyrosine. Using the isotope-labeling technique, *Curtius et al.* also investigated the degradation pathways of a series of aromatic carboxylic acids under the action of the intestinal flora. The use of stable isotopes of carbon[231], oxygen[232], nitrogen, *etc.*, is to be preferred to deuterium labeling in such studies, because of the substantially smaller isotope effects in *in vivo* transformations and because of the very stable incorporation of these atoms.

9. GC-MS as a Reference Method for Quantitative Determinations

Because of its sensitivity and range of application, the GC-MS combination competes with a number of other methods in quantitative determinations: gas chromatography, preferably with an electron-capture detector, radioimmuno methods[233], and fluorometric and photometric processes. *Björkhem et al.*[234] compared the determination of the urine estriol concentration by three methods. The estriol concentration in the urine of pregnant women is followed as a routine measure in pregnancies at risk, since it gives important information on possible complications. The authors used GC-MS as a reference method to check two simpler processes in clinical biochemistry. As the internal standard they used dideuterated estriol, which was converted into the trimethylsilyl derivative *(29)* for the GC separation.

After the construction of a standard curve, quantitative determinations in the concentration range of 2—50 μg/ml urine could be performed with a relative standard deviation of 6 %. In routine clinical analysis the concentration of estriol is generally determined by gas chromatography or photometrically. For a comparison, samples were analyzed by GC-MS, by GC alone, and photometrically. Figure 13 shows the correlation between the results of GC-MS and GC alone.

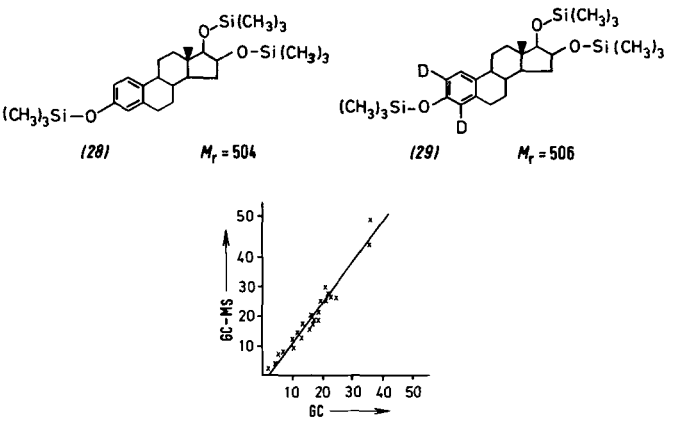


Fig. 13. Comparison of the analytical values in the quantitative determination of estriol by a gas-chromatographic method and a GC-MS combination (numerical values everywhere in [μg/ml]). The correlation coefficient of the results is 0.97 (after [234]).

The investigation showed that the routine methods used for estriol are sufficiently accurate and specific. It may be concluded from a series of comparative quantitative investigations[235–243] with the methods mentioned above that, because of its high specificity, GC-MS can in many cases be used for controlling simpler routine processes. Likewise, in testing new quantitative assays it is often a reliable reference method.

10. Quantitative Measurements with Modern Ionization Techniques

10.1. Atmospheric-Pressure Ionization (API)

Atmospheric-pressure ionization[244–247] is a variant of chemical ionization in which the ion source is at atmospheric pressure. The sample substance (which may include a solvent) is evaporated in the heated inlet system under normal pressure and then passes rapidly into the neighborhood of a very small opening which leads to the analyzer section held under high vacuum. On the normal-pressure side of the opening primary ions are produced in the gas by a radioactive source or by an electric discharge, and these form ions from the sample molecules by a series of secondary ion-molecule reactions. Both positive and negative ions are produced, which pass with the pressure gradient into the analyzer section

together with neutral particles. There the ions are accelerated by electric lenses and are focused into an ion beam.

Since according to the principle of chemical ionization negative ions can be obtained in relatively high yields, an example may be given here in which negative ions were used for a quantitative determination. *Horning et al.*[28] determined the concentration of the drug diphenylhydantoin *(30)* in samples of human plasma by API mass spectrometry. The authors used the triply-^{13}C-labeled compound *(31)* as an internal standard, carried out extraction with dichloromethane, and injected part of this extract without preliminary separation into the inlet system of an API mass spectrometer. Figure 14 shows the mass spectrum obtained.

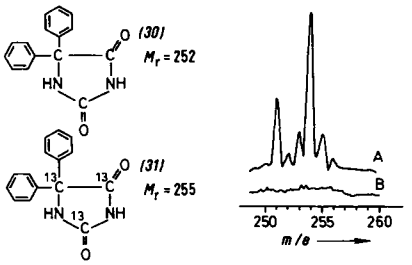


Fig. 14. API mass spectrum of the negative ions of a plasma extract (A) and the corresponding blank (B) of the pure solvent dichloromethane. The two intense ions are the $[M-1]^-$ ions of the drug diphenylhydantoin *(30)* (m/e=251) and of the ^{13}C-labeled internal standard *(31)* (m/e=254). The signal of the internal standard corresponds to an absolute amount of substance of 480 pg. The concentrations of sample and standard were respectively 10.4 and 24 μg/ml plasma. The quadrupole mass spectrometer was used for detection by repetitive scanning of the range m/e=245—260. The results were recorded by a computer and presented at the end of the analysis (after [28]).

In the case of the diphenylhydantoins only the $[M-1]^-$ ions appear in the API spectrum of negative ions. Because of the relatively high plasma concentration, it was possible to perform a quantitative determination without preliminary separation (cf. Section 6.3). This method is so sensitive that the part of the sample investigated corresponded to a content of only 20 nl of plasma. For combining API with a method of separation, its direct coupling with a liquid chromatograph has been described[248].

10.2. Field Ionization (FI)

The principle of field ionization[249–251] consists in the detachment of an electron from organic molecules in an extremely high electric field (several 10^7 V/cm). In this method of ionization only a relatively small amount of excitation energy is transferred, so that the field-ionization mass spectra show a lower relative intensity of the fragment ions and a higher relative intensity of molecular ions in comparison with electron impact mass spectra[246, 247]. In comparison with EI and chemical ionization, field ionization yields considerably smaller ion currents. In relation to the sensitivity of the FI method, this disadvantage is compensated to some extent by the fact that the few ion species occurring in the FI spectra carry a high proportion of the total ion current. *Reynolds et al.*[118] increased the sensitivity of FI by two modifications: they used a special emitter localized in the immediate neighborhood of the direct inlet system for the ion production and

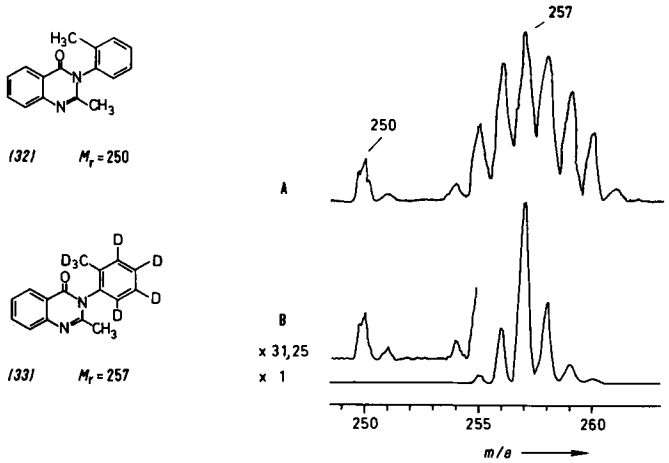


Fig. 15. FI mass spectrum of the molecular ion group of methaqualone *(32)* and [D_7]-methaqualone *(33)*, recorded by a multi-channel analyzer with ion counting. A) Logarithmic recording; B) linear recording at various sensitivities; the more sensitive trace corresponds to maximum scale deflection of 256 ions, and the less sensitive one to a maximum scale deflection of 8000 ions. The concentration of the unlabeled compound *(32)* was found to be 20 mg/ml urine. The urine extract was purified by chromatography and evaporated *via* the direct inlet (after [118]).

a multichannel analyzer for counting the ions. In this way, with an internal standard, the above authors were able to determine the drug methaqualone *(32)* in urine samples down to a concentration of a few ng/ml. Figure 15 shows an FI mass spectrum recorded for the quantitative determination.

The investigation demonstrated that with special methods of ion detection even with relatively weak ion currents it is possible to perform sensitive quantitative determinations.

10.3. Field Desorption (FD)

In field desorption, as in FI, the ions are produced in a strong electric field. However, the sample is not supplied to the emitter through the gas phase, as in FI, but at the beginning of the analysis it is present in the adsorbed state on the emitter surface. Field desorption permits gentle ionization of highly polar compounds and those of low volatility[252, 253], especially of salts[254–256], since there is no separate evaporation process of the sample. The mass spectra frequently show only the molecular ion or a cluster ion formed by the attachment of a cation to the molecule. Protons and especially alkali metal cations[257–259], are suitable for this process (cationization). For this reason the molecular ion group frequently carries the total current in FD, which is a favorable situation for quantitative analysis since it gives optinum sensitivity and reduces the disturbances due to impurities, and in addition no structurally significant fragments are necessary.

The often very short-lasting, and in the case of polar compounds also fluctuating, ion currents in field desorption demand integrating recording for a quantitative determination. Investigations with photographic[260–263] and electrical[262, 264–266] recording have shown that it is possible to carry out quantitative measurements by field desorption with good precision by using standards labeled with stable isotopes. Figure 16 shows the first results of the quantitative determination of cyclophosphamide *(17)* with the use of a deuterated standard *(34)*.

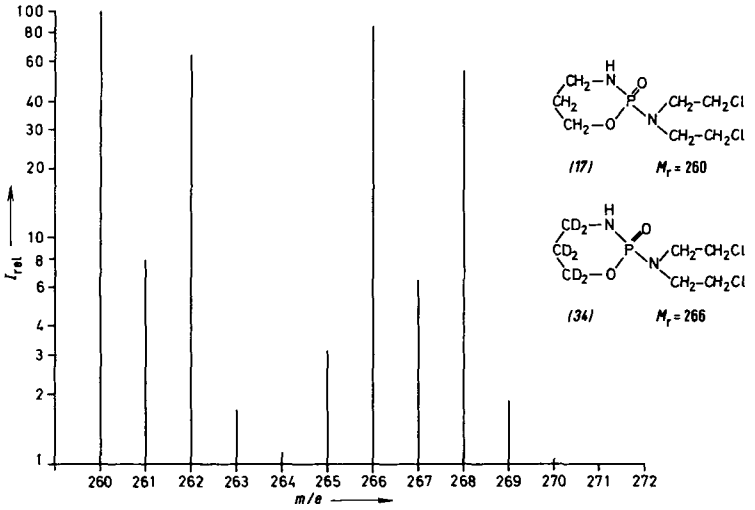


Fig. 16. FD mass spectrum of the molecular ion group of a mixture of $[D_0]$-cyclophosphamide *(17)* and $[D_6]$-cyclophosphamide *(34)* in the ratio of 1:0.85. Photographic detection with a resolution of about 15000 was used for recording the spectrum. Quantitative evaluation of the degree of blackening gives values with errors of about 5 % (after [260]).

By means of high-resolution mass spectrometry the specificity of mass-spectrometric detection can be raised to such an extent that quantitative determinations in untreated biological samples actually become possible (see Section 7.2). Figure 17 shows the desorption profile of a model mixture of homovanillic acid *(35)* and its isotopically labeled analog *(36)* obtained by high-resolution FD-MS.

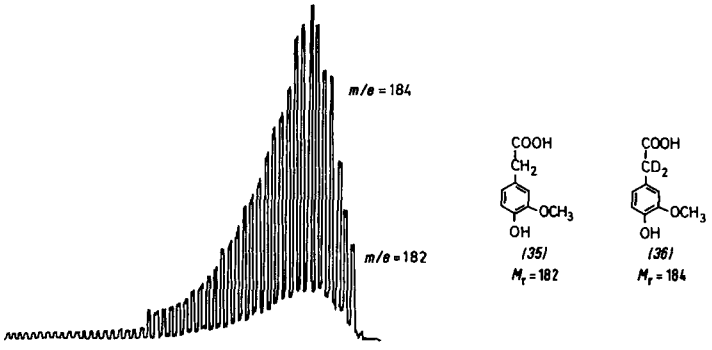


Fig. 17. Quantitative high-resolution FD mass spectrometry of $[D_0]$-homovanillic acid *(35)* with $[D_2]$-homovanillic acid *(36)* as internal standard. The desorption profiles were recorded with a linear increase in the emitter heating current and variation of the accelerating potential. The sample mass was 400 and 100 ng, respectively, at a mass spectrometric resolution of 12000. *(35)*:*(36)* (theoret.) = 1:4.35; *(35)*:*(36)* (exp.) = 1:4.60 (+5.7 %). (This determination was performed with a double focusing Varian MAT 731 mass spectrometer.)

Integrating recording of FD ion currents for quantitative measurements is most advantageously performed by the use of a multi-channel analyzer which accumulates the signals and thus averages the relative intensities. This technique permits direct isotope analysis of labeled and unlabeled organic molecules[268], which is demonstrated in Figure 18 for the protonated molecule of the antitumor drug methotrexate.

When analyzing natural products containing a large number of carbon atoms (>50) the precision of such a direct isotope analysis is sufficient to detect a slight natural depletion in

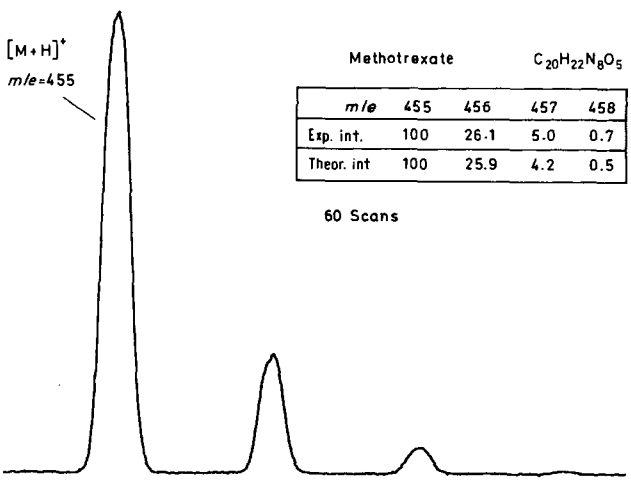


Fig. 18. $[M+H]^+$ ion group of methotrexate, recorded by FD-MS and accumulation of 60 cyclic magnetic scans. Good agreement is found between the observed relative intensities and those calculated from the natural isotopic abundances.

the ^{13}C abundance[268]. This effect is also found in a precision isotope analysis of carbon from plant material[23, 225].

FD-MS shows an extremely high sensitivity for organic and inorganic cations, especially for alkali metal cations[269, 270]. Therefore, even complex mixtures containing these ions in ppb concentrations can be analyzed successfully without pretreatment[271]. Precise and sensitive determination of the trace element lithium, which is used for the chemotherapy of some affective disorders, is an example of metal analysis in the biomedical field. Figure 19 shows the determination of the normal lithium level in human plasma, which has been performed by stable isotope dilution and accumulation of the FD ion currents with a multi-channel analyzer.

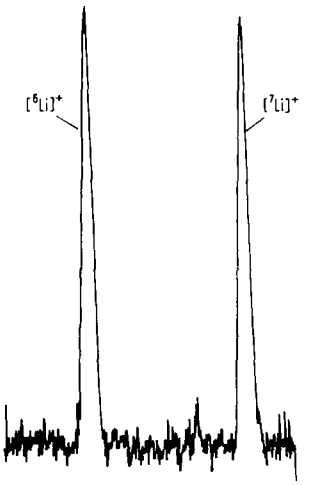


Fig. 19. Original trace of a $[Li]^+$ determination by FD-MS. 23 cyclic magnetic scans were accumulated by a multi-channel analyzer. A known amount of an isotopically enriched lithium salt was used as internal standard. Standard: ^6Li 88.4 %; ^7Li 11.6 %. Natural abundance: ^6Li 7.5 %; ^7Li 92.5 %. Quantitative evaluation gave a lithium concentration of 13.4 µg/l in the human plasma investigated. The sample amount for the measurement was 2 µl plasma.

For a quantitative analysis of organic compounds sample amounts between one nanogram and some micrograms are sufficient—depending on the purity of the sample and the compound under investigation. The sensitivity for a number

of organic and inorganic cations is about three orders of magnitude higher. The results obtained so far show that FD-MS is a useful method for assessing quantitative problems in the area of biochemistry and medicine[267, 272].

11. Evaluation and Prospects

Specific, sensitive, and quantitative detection of low-molecular biochemically important compounds in biological samples is possible with the aid of mass spectrometry. The main impetus for the expansion of quantitative analyses with the mass spectrometer in recent years came from the greater availability of compounds labeled with stable isotopes that are required as internal standards for quantitative determinations. The unobjectionable stable isotopes can generally replace radioactive isotopes in many *in vivo* investigations on human subjects, since sensitive mass-spectrometric methods are available for the detection of stable isotopes. A wide application of the method is opposed by the relatively high costs of the purchase and operation of a mass spectrometer. In addition to this, today in general there are the costs of a data-processing system, which are of the same order as those of the spectrometer itself. This expenditure is justified by the versatility of the combined system, which allows the solution of analytical problems in biochemistry and medicine that would otherwise be difficult or impossible. For these reasons a rapid further development and successful use of quantitative mass spectrometry in the described fields must be expected.

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Photoacoustic Spectroscopy of Condensed Matter

New analytical methods (11)

By R. B. Somoano[*]

Photoacoustic spectroscopy is a new analytical tool that provides a simple nondestructive technique for obtaining information about the electronic absorption spectrum of samples such as powders, semisolids, gels, and liquids. It can also be applied to samples which cannot be examined by conventional optical methods. Numerous applications of this technique in the field of inorganic and organic semiconductors, biology, and catalysis have been described. Among the advantages of photoacoustic spectroscopy, the signal is almost insensitive to light scattering by the sample and information can be obtained about nonradiative deactivation processes. Signal saturation, which can modify the intensity of individual absorption bands in special cases, is a drawback of the method.

1. Introduction

Photoacoustic spectroscopy (PAS) is a new analytical tool that provides scientists with information about the electronic absorption spectrum of solids, semisolids, gels, and liquids. The photoacoustic effect (PA effect) was first discovered by *Alexander G. Bell* in 1881[1], but interest in the phenomenon subsequently waned. Recently, however, renewed interest in the PA effect in solids has emerged and it has been demonstrated that PAS may be a very useful analytical technique for the study of condensed matter. Much of this initial work was done by *A. Rosencwaig* of Bell Laboratories[2]. The purpose of this article is to give a state-of-the-art description of PAS which will illustrate its usefulness and limitations. Some of the more interesting and important results of concern to the nonspecialist will also be described in this article.

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2. The Photoacoustic (PA) Effect

In a typical PA experiment, a sample is enclosed in an airtight non-resonant cell along with a sensitive microphone (Fig. 1a). The cell also contains air or any other gas at atmospheric pressure. The sample is illuminated with periodically modulated monochromatic light of wavelength λ. A typical modulation or chopping frequency f is 100 Hz. If the sample absorbs light of wavelength λ, electrons will be excited to higher states (Fig. 1b). After a brief time, the electrons decay back to the ground state by radiative and/or nonradiative processes (Fig. 1c). The PA effect is due solely to the *nonradiative decay processes*. When the electrons decay nonradiatively, a periodic heat distribution (of frequency f) is created in the sample at the point of absorption. This thermal distribution then diffuses throughout the sample in all directions (Fig. 1a). That part of the heat which diffuses to the sample surface gives up its thermal energy to the surrounding air. Only a very thin ($\approx$1 mm) boundary layer of air responds to this heat input and it periodically expands and contracts as it

is heated and cooled at frequency f. This thin layer of air then acts as an acoustic piston on the remaining column of air, creating pressure fluctuations which are detected by the microphone as the PA signal.

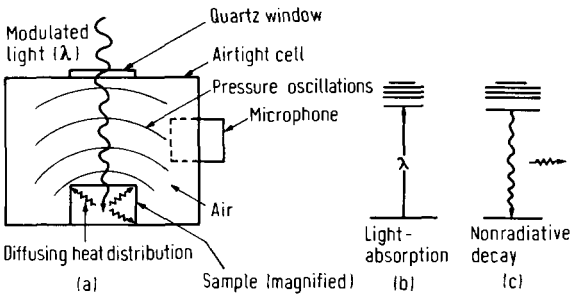


Fig. 1. A schematic of the photoacoustic (PA) effect. a) Diffusing heat distribution (⇝) and detection of the pressure fluctuations (the PA signal). The sample size relative to the cell and microphone has been magnified in order to show the diffusing thermal distribution. b) Light absorption and c) nonradiative de-excitation (cause of heat flow).

Thus, the PA process may be summarized as follows: 1) Absorption of periodically modulated light of wavelength λ; 2) nonradiative decay to create a periodic heat distribution; and 3) thermal diffusion to the sample-air interface to create pressure fluctuations (the PA signal). At wavelengths where no absorption occurs, no PA signal will be created. Thus, the PA signal correlates with the optical absorption and a plot of the microphone output *versus* λ gives the absorption spectrum.

There are several important features of the PA process:

1) In contrast to conventional optical spectroscopy, the PA effect is dependent upon both the excitation of excited states as well as their decay processes. If excited electrons decay solely by radiative modes (*i.e.*, if they fluoresce strongly), no PA signal will be generated. Hence, PAS provides information about the nonradiative decay modes and serves as a complementary tool to fluorescence spectroscopy.

2) The PA signal is quite insensitive to light scattered by the sample. Unlike conventional optical spectroscopy where scattered light gives rise to unwanted and misleading signals, in PAS only the absorbed light leads to a PA signal. Scattered light affects the PA signal only indirectly by reducing the amount of light incident upon the sample which might be available for absorption. This is of consequence only in very weakly absorbing or highly reflecting samples[3].

3) Because of the thermal diffusion process the photoacoustic signal is dependent upon both the optical and thermal properties of the sample. This feature is quite important and leads to certain limitations of PAS, such as signal saturation which will be discussed in Section 5.

Several other points concerning the PA effect should be mentioned. The effects of sample mass, particle size, sample reflectivity, and the use of gases other than air have been studied[4, 5]. Very small sample masses ($\approx 10^2$ μg) may be used. The PA signal increases at all wavelengths as the particle size decreases because power absorption and thermal transfer efficiency improve as the surface area increases. Thus, a finely ground sample will yield a larger PA signal than a single crystal or polycrystal of the same material. Highly reflecting samples are undesirable and must usually be ground to improve sample absorption. Finally, gases other than air offer no significant improvement although the use of higher pressures should enhance the signal.

In summary, PAS is a simple nondestructive technique providing qualitative information about the electronic absorption spectrum of samples such as powders, gels, semisolids, and liquids which might otherwise be unsuitable for study by conventional optical techniques.

3. Experimental Apparatus

The apparatus required to detect the PA effect is quite simple. The basic components are: light source, monochromator, PA cell, microphone, associated optics (lenses and mirrors), and electronics. Figure 2 shows a schematic drawing of a typical apparatus. A reasonable PA signal is only obtained with a sufficiently intense light source. Therefore, most PA spectrometers utilize a 1000 W xenon source although sources

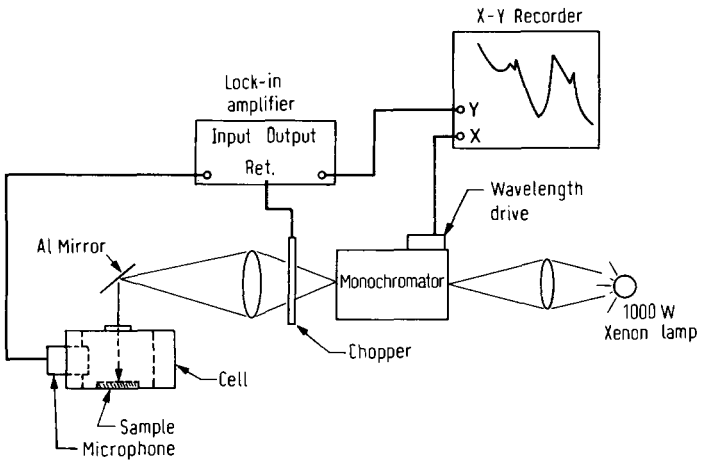


Fig. 2. Schematic of a single beam photoacoustic spectrometer.

of 350 watts or greater will also give reasonable PA signals if all other components are optimized. (The reason for using a xenon source will be discussed later.) To achieve a high light throughput, the monochromator is usually a $\frac{1}{4}$ meter instrument with a large f-stop (*e.g.*, f/3). A wavelength drive can be mounted on the monochromator. An important requirement for the PA cell is that the sample chamber volume be small (a few cm^3) and airtight. The small volume enhances the effects of pressure fluctuations, and hence the PA signal. The cell may be made of stainless steel, brass, aluminum, lucite, *etc.* Each material has certain advantages and disadvantages, depending upon its reflectivity and absorption spectrum and the nature of the samples to be studied. If absorption data below 300 nm are desired, quartz lenses and windows are required. The sample may be loaded horizontally or vertically into the cell. The cell should be so designed that it may be disassembled for occasional cleaning.

Microphones for use in a PA cell are usually $\frac{1}{2}$" to 1" in diameter and of either an electret or condenser design. The microphone is a crucial element of the apparatus and should have a flat frequency response between 10—10^4 Hz. The voltage output of the microphone is fed into a phase-sensitive lock-in amplifier for amplification and signal processing and then to an X-Y recorder. The phase of the PA signal

(with respect to the reference signal from the lock-in amplifier) is usually adjusted to maximize the PA signal at some arbitrary wavelength.

There exists considerable flexibility in the arrangement of the components described above. For example, the chopper might be placed between the monochromator and light source, a laser may be used, the arrangement of the microphone with respect to the sample can be varied, *etc.*

The apparatus just described is essentially a single beam instrument, and the spectral structure of the light source at various wavelengths will thus be superimposed on the sample spectrum. To correct this, one first runs a spectrum of a highly opaque sample such as carbon black. The PA signal will be in the saturation regime (see Section 5) and hence constant with wavelength. The only structure in a carbon black PA spectrum will therefore originate from the xenon light source. One then runs the sample spectrum and removes the light source structure by dividing the sample spectrum by the carbon black spectrum. This may be done point by point, by hand or with a small computer. An alternative method is to utilize a double beam instrument in which the light beam is split between the sample and a carbon black reference. A xenon light source is preferred because it is quite intense in the visible-UV region with relatively little structure, and this facilitates the normalization procedure. With a xenon light source, PA spectra may be obtained from 230 to *ca.* 1500 nm. At the present time, there are no light sources sufficiently intense in the IR (other than lasers) to provide PA spectra in this region.

4. Applications

Althogh PAS is still in its infant stage, numerous exciting and important applications in various scientific fields have already emerged. These new applications were motivated by the ubiquitous need to obtain qualitative information about the electronic excitation spectrum in a simple, quick, nondestructive manner for samples in various physical states (*e.g.*, crystalline, amorphous, gel, *etc.*). As long as the sample is not highly reflecting, PAS will give information about the bulk electronic excitation spectrum. The samples may be inorganic or organic, metals, semiconductors, or insulators.

4.1. Inorganic and Organic Semiconductors

An example of the use of PAS to study some rather conventional materials involves the investigation of inorganic semiconductors. Figure 3 shows PA spectra of several well-known semiconductors. The sharp increase in the PA signal is due to transitions between the valence and conduction bands. The arrows mark the position of the "knee" in the PA spectrum which corresponds to the value of the absorption edge, or energy gap, of the semiconductor. Values of the energy gap obtained by conventional means are shown in parenthesis. Several points concerning these spectra should be made: 1) The PA technique gives the correct spectrum for both direct (CdS) and indirect (GaP) bandgap semiconductors; for GaP, both kinds of band gap transitions are revealed; 2) the samples consist of powders taken off the shelf without further purification, or single crystals which were ground up to reduce the reflectivity and increase the surface area; 3) the sample mass was a few milligrams; and 4) each spectrum was obtained in a few minutes. These points emphasize the ease and convenience with which data of importance for the optical and

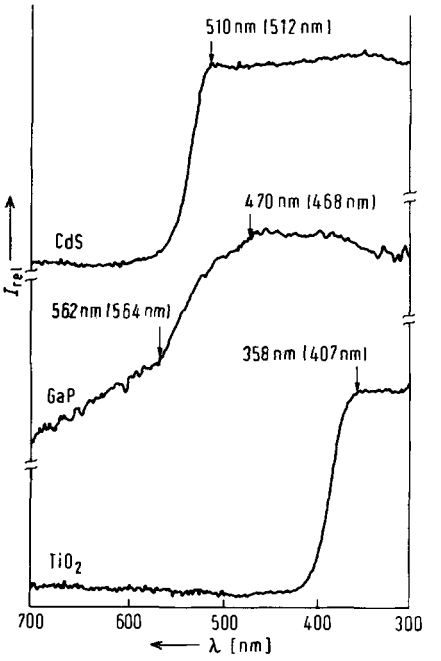
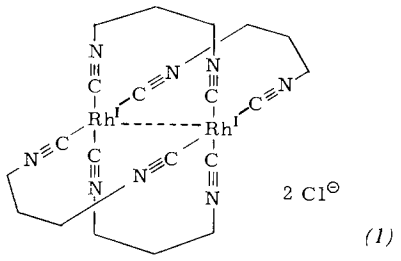


Fig. 3. Photoacoustic spectra of the inorganic semiconductors CdS, GaP, and TiO_2. The arrows indicate the location of the absorption edge. The numbers in parentheses indicate values of the absorption edge obtained by conventional means. The two values for GaP correspond to the indirect band gap (562 nm) and the direct band gap (470 nm).

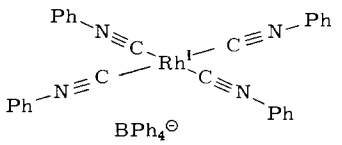
electrical properties of semiconductors may be obtained without the need for high purification or high vacuum techniques. In addition, one can differentiate between different crystalline phases of the same material, such as the rutile and anatase phases of TiO_2[6]. By utilizing PAS at low temperatures, it should be possible to detect excitonic structure as well as the occurrence of phase transitions. The above semiconductors are also of interest for use as electrodes in photoelectrochemical cells to convert solar energy into electrical and chemical energy. Thus, PAS provides a convenient tool for the physicist or chemist to quickly screen, characterize, and correlate the optical properties of numerous semiconductors for use in new and novel systems.

Organic and organometallic semiconductors may also be investigated using PAS. These materials are of interest in the field of quasi-one-dimensional (1 D) conductors. The compounds consist of weakly coupled chains of molecular units and may exhibit very high electrical conductivity parallel to the chains. The compounds may be metallic if the atoms or molecules are uniformly spaced along the chain. However, quasi-one-dimensional metallic chains are fundamentally unstable with respect to certain lattice distortions (*Peierls'* instability). Thus, in some compounds the chains will distort in such a manner that the atoms or molecules form dimers, trimers, tetramers, *etc.* This distortion, or transition, can occur at temperatures above or below room temperature. The compounds with distorted chains are semiconductors since the nonuniform spacing of the molecules along the chain opens up a gap at the Fermi level in the electronic energy spectrum.

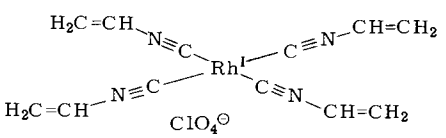
Thus, the electrical and magnetic properties are crucially dependent upon the chain structure. The compounds are usually darkly colored powders. Single crystals, which are difficult to obtain, take the form of very small needles (a few mm long) making conventional optical studies very difficult.



(1)



(2)



(3)

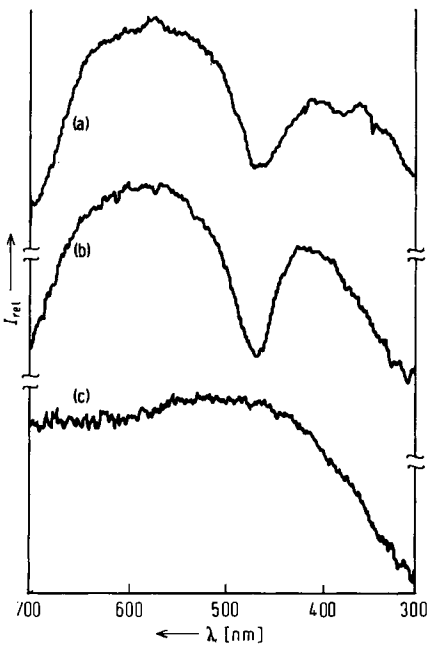


Fig. 4. Photoacoustic spectra of several organorhodium compounds. a) Dirhodium complex *(1)*; b) rhodium complex *(2)*; c) rhodium complex *(3)*. The absorption band at 575 nm in (a) and (b) is associated with the formation of dimers.

PAS may be utilized to gain an insight into the structural characteristics of these materials. Figure 4 shows the PA spectra of several rhodium organometallic compounds. Figure 4a shows the PA spectrum of an interesting rhodium-"bridged" dimeric compound *(1)*, in which the rhodium atoms are physically bound into a dimeric structure by bridging ligands. The bridging dimers are not part of a chain structure in this compound. However, the interesting feature is the presence of the strong absorption band at 575 nm which is due to the dimeric structure[7]. A similar band is found in the solution spectrum. Figures 4b and 4c show PA spectra of the rhodium compounds *(2)* and *(3)*. The rhodium atoms are square planar coordinated by isocyanide ligands, (R—CN), and stack to form rhodium chains in contrast to the dimer *(1)*. Nevertheless, the PA spectra of tetrakis(phenyl isocyanide)rhodium tetraphenylborate *(2)* (Fig. 4b) reveals the same strong rhodium-rhodium band at 575 nm indicating a dimeric chain structure. The room temperature electrical conductivity of this material is quite low ($\sigma \approx 10^{-10}\,\Omega^{-1}\,cm^{-1}$) as would be expected for the nonuniform (dimeric) spacing along the chain. In contrast, the PA spectrum of tetrakis(vinyl isocyanide)rhodium perchlorate *(3)* (Fig. 4c), does not reveal any sign of the dimer, suggesting that this material contains chains of uniformly spaced rhodium atoms. Indeed, the electrical conductivity of this compound at room temperature ($\sigma \approx 2\ \Omega^{-1}\cdot cm^{-1}$) is the highest known for any rhodium chain complex[8]. All of the structural information deduced from the PA spectra of Figure 4 have been fully confirmed by single crystal x-ray diffraction studies[8]. Similar results have been obtained on iridium chain complexes[9].

In summary, PAS provides a very simple technique for gaining an insight into the structural and electrical properties of quasi-1D conductors without having to grow single crystals or perform X-ray measurements. In this way, many new potentially conducting compounds may be screened without the expenditure of excessive time and funds.

4.2. Metals

PAS may be used to study metals if the reflectivity is first diminished by grinding or through the use of powders. Because

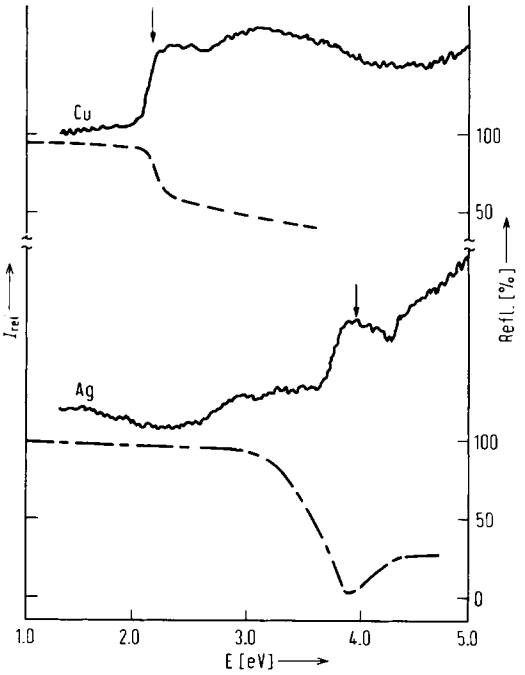


Fig. 5. Photoacoustic spectra of copper and silver (from ref. [2]). The arrows mark the location in the PA spectrum where reflection loss occurs. The normal reflectivities of Cu (---) and Ag (–·–) as measured by conventional means are also shown [vertical scale ("Refl.") on the right side of the figure].

of the very large absorption coefficients of metals, the absorption spectrum cannot be obtained by PAS (see Section 5); however, the presence of the metal (*e.g.*, on a surface) may be detected by its loss of reflectance which may result from interband transitions, a plasma resonance, *etc.* Figure 5 shows the PA spectra of Cu and Ag as well as their normal reflectivity. The sharp structure in the PA spectra as indicated by the arrows occurs at the point of reflection loss and can serve as a signature for the presence of a particular metal. The structure in the PA spectra also emphasizes the care one must take in the choice of materials for use in the construction of a PA cell (see Section 3).

4.3. Biological Studies

One of the most promising areas for the use of PAS is in the study of biological systems. Many biological samples contain water, proteins, and other lipid materials which readily scatter light, thus hindering the use of conventional optical techniques. Extensive extraction processes are required to separate out the material of interest for study by ordinary optical methods. Since scattered light is not a serious problem in PAS, biological samples may be readily studied, without extensive processing, by this technique. An example is the detection and study of oxyhemoglobin in human blood. Fig. 6 shows

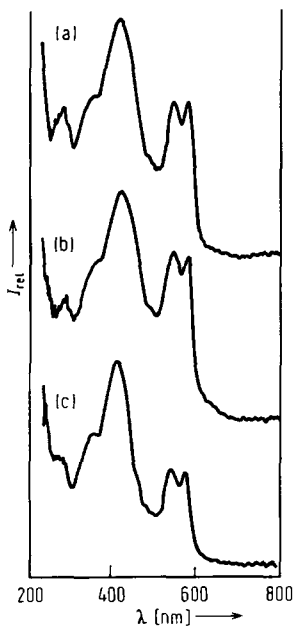


Fig. 6. Photoacoustic spectra of human blood after various stages of processing. a) Whole blood; b) whole blood after plasma removal; c) extracted hemoglobin (→ oxyhemoglobin).

the PA spectra of human blood after various stages of processing[2]. The sample in Figure 6a is simply a smear of whole blood, while the samples in Figures 6b and 6c are of red blood cells freed from plasma and of extracted hemoglobin, respectively. The characteristic spectrum of oxyhemoglobin is quite apparent and the time consuming extraction processes normally used to obtain a blood sample suitable for study by conventional optical means have been eliminated. Similar studies may be carried out on other hemo-proteins such as cytochrome c and catalase[6] with considerable ease.

Complex biological systems such as intact plant matter may be conveniently studied by PAS. Figure 7 shows the PA spectrum of dried spinach leaf and reveals the chlorophyll bands at 450 and 650 nm. Thus, plant growth mechanisms and abnormal processes may be studied in intact and living matter by PAS.

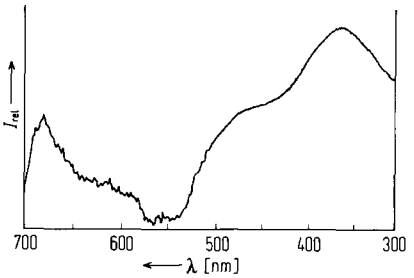


Fig. 7. Photoacoustic spectrum of spinach leaf.

Another use of PAS is in the identification of various bacterial states. It is quite difficult to examine bacterial cultures by conventional optical means because of excessive light scattering by the bacteria. However, the samples are quite suitable for study by PAS. The PA spectrum of *Bacillus subtilis Var. niger* (a common airborne bacterium) in the spore state contains a strong absorption band at 410 nm. This band is absent when the bacterium is in the vegetative state. Thus, PAS enables the detection and discrimination of various bacterial states and allows one to characterize, monitor, and detect bacteria in various stages of development.

PAS may also be used in the study of human and animal tissues in order to obtain valuable information about pathology and disease processes. Only a few examples of PA studies of biological systems have been mentioned here. Yet PAS will probably find its greatest use in the fields of biology and medicine.

4.4. Studies on Catalysis and Chemical Reactions

An important area where PAS is being utilized at present is in the study of photochemical processes and catalysis. An example involves the investigation of the reaction of transition metal complexes with polymeric ligands to form anchored catalysts which have been used to catalyze hydrogenation and hydroformylation of olefins. PAS has been used to investigate the electronic structure of these metal-polymer complexes in order to elucidate chemical processes and structure-reactivity relationships. An example of a PA study of a model catalytic system involving a well characterized compound, hexacarbonyltungsten $W(CO)_6$, is shown in Figure 8.

The PA spectrum of $W(CO)_6$ is shown both before and after photochemical reaction with polyvinylpyridine. Figure 8a shows the PA spectrum of $W(CO)_6$ and reveals the singlet-triplet ligand field transition at 350 nm as well as the corresponding singlet-singlet transition at 310 nm[10]. Figure 8b shows the PA spectrum of $W(CO)_5L$, where the ligand L is NH_3. This compound is formed upon irradiation of $W(CO)_6$ in the presence of the ligand and is shown in order to demonstrate the effect of ligand substitution in $W(CO)_6$. The characteristic singlet-triplet and singlet-singlet transitions at 457 and 416 nm, respectively, of $W(CO)_5NH_3$[10] are observed in the

form of a broad absorption band from 375 to 475 nm. Figure 8c shows the PA spectrum of the photoproduct of $W(CO)_6$ and polyvinylpyridine and clearly reveals the $W(CO)_5$-pyridine absorption band similar to that seen in Figure 8b. The polymer-anchored $W(CO)_5$ species has been observed to catalyze olefin isomerization and hydrogenation[11]. Thus, PAS may be used to study and characterize solid state photoproducts where conventional optical and structural (*i.e.*, X-ray) techniques would be totally inadequate.

An example of a less well understood, but potentially useful polymer anchored catalyst involves the transition metal cluster complex, dodecacarbonyltetrarhodium, $Rh_4(CO)_{12}$. Figure 9 shows the PAS of (a) $Rh_4(CO)_{12}$, (b) the photoproduct of the reaction of $Rh_4(CO)_{12}$ solution with polyvinylpyridine, and (c) the thermal product (*i.e.*, as for (b) but not exposed to UV radiation). The polymer-metal complexes of Figures 9b and 9c are both found to be hydroformylation catalysts, but the phototriggered catalyst (Fig. 9b) is considerably more active. This extra activity is associated with an absorption band (shoulder) at 600 nm which is absent from the spectrum of the less active thermal catalyst. Upon prolonged exposure

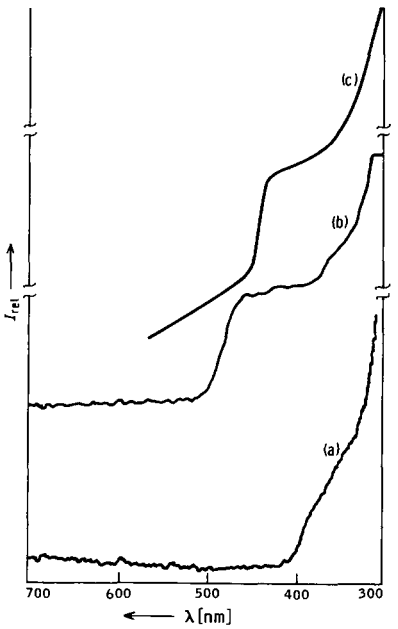


Fig. 8. Photoacoustic spectra of hexacarbonyltungsten complexes. a) $W(CO)_6$; b) $W(CO)_5NH_3$; c) $W(CO)_6$ polyvinylpyridine complex. The complexes in (b) and (c) are photoproducts.

to air, the phototriggered catalyst decomposes as indicated by the loss of the 600 nm absorption. Its PA spectrum then resembles that of the thermal catalyst and exhibits correspondingly less catalytic activity[12]. Similar studies are being carried out with $Co_4(CO)_{12}$.

Another use of PAS in this field has been to detect the degree of reduction of metals reacted on polymeric substrates. By using PAS to monitor the reaction of, say, potassium tetrachloroplatinate with polyvinylpyridine, one may easily tell when the tetrachloroplatinate has been fully reduced to platinum metal. The use of PAS in catalysis studies is just starting, but there is every indication that it will prove to be a valuable tool.

PAS has also been used for the study of chemically treated controlled pore glasses. These materials are growing in importance in the fields of chemical synthesis and analysis. Functional groups such as metal chelation reagents, acid-base indicators, and enzymes can be attached to the surface of the glass and used in a variety of chemical reactions. However, techniques for definitive characterization of the attached functional groups are rather primitive and ineffective. PAS has been used to determine the presence of these groups and to monitor subsequent chemical reactions and identify photochemical degradation processes.

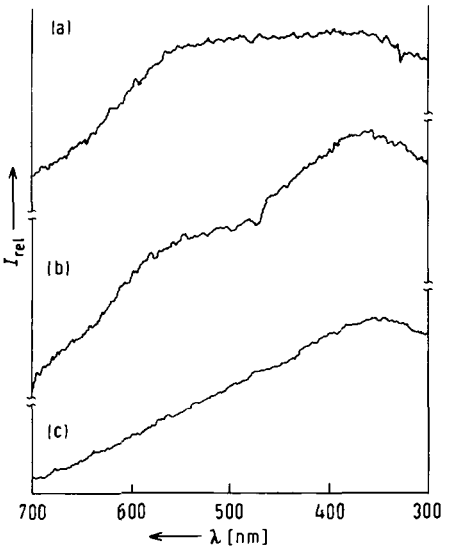


Fig. 9. Photoacoustic spectra of dodecacarbonyltetrarhodium complexes. a) $Rh_4(CO)_{12}$; b) photoproduct of reaction of $Rh_4(CO)_{12}$ solution with polyvinylpyridine; c) same as for (b) but not irradiated with UV light (*i.e.*, a thermal product).

Numerous other applications of PAS (*e.g.*, de-excitation studies of fluorescent systems and surface studies) have been discovered and the reader is referred to the literature for additional information[2, 6].

5. Limitations of PAS

There are several limitations to PAS which result in its being a less quantitative tool than conventional spectroscopic techniques. For example, one is not able to measure absorption coefficients conveniently and, in some cases, the PA spectra may contain structure due to both absorption and reflection losses. Also, the lack of suitable light sources prevents PA studies in the far IR. However, the main limitation of PAS is signal saturation[5] and arises from the contribution of thermal diffusion processes to the PA effect. Since this limitation is quite important and provides additional insight into the PA effect, it will be described briefly.

Consider a sample in a PA cell with cylindrical geometry (Fig. 10). The illuminated surface is also the surface for thermal transfer to the surrounding gas. The sample is characterized by an optical absorption coefficient β [cm^{-1}], which is a function of wavelength. The sample surface is irradiated by periodically modulated light of intensity I where I_0 is the

$$I = I_0 \cos \omega t,$$

incident light flux from the monochromator, and $\omega = 2\pi f$ is the modulation frequency in radians/s. The optical power absorbed by the sample is proportional to

$$\beta e^{-\beta l} I_0 \cos \omega t$$

where l is the distance into the sample from the illuminated surface where optical absorption occurs.

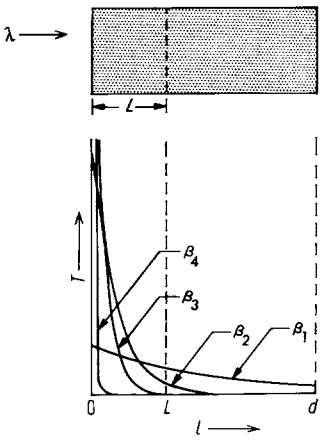


Fig. 10. Schematic of a sample model and the magnitude of the initial heat distribution. β_1 corresponds to nonzero transmission, β_2 to transmission approaching zero but before saturation, $\beta_3 = a_s$ to the onset of saturation, and finally β_4 to approaching full saturation. $L = 2\pi/a_s$ (see text).

When a state excited during absorption decays thermally (*i.e.*, non-radiatively) a periodic increase in the temperature occurs at the point of optical absorption. Thus, an initial heat, or temperature, distribution is created in the sample whose magnitude is also proportional to $\beta e^{-\beta l}$ and periodic with frequency ω. This initial heat distribution will diffuse away from its source (the point of optical absorption) in all directions. However, its initial magnitude will be diminished by a factor of $e^{-a_s x}$ due to thermal damping processes as it diffuses throughout the solid. The term a_s is the thermal diffusion coefficient in cm^{-1}, and is given by

$$a_s = (\omega/2\alpha_s)^{1/2} \qquad (1)$$

where α_s is the thermal diffusivity in cm^2/s and x is the distance from the point of optical absorption. Thus, only that portion of the sample within a distance $L = 2\pi/a_s$ of the thermal transfer surface will be effective in transferring its thermal energy to the surrounding gas. Those portions of the sample deeper than L cannot contribute to the PA signal because of thermal damping. The distance into the sample for which optical absorption takes place is governed by optical damping (*i.e.*, the optical absorption coefficient β in $e^{-\beta l}$). For low values of β, (*e.g.*, β_1 in Fig. 10) much of the heat distribution is created outside of L and cannot contribute, resulting in a low PA signal. As β increases, to say, β_2, the initial heat distribution moves into the region bounded by L (as well as closer to the thermal transfer surface) and a larger PA signal occurs. Thus, the variation of the PA signal with β occurs because the initial heat distribution moves in and out of the "responsive" region bounded by L as β varies. For $\beta = \beta_3 = a_s$, all of the heat distribution is created within L and further increases in β only move the distribution closer to the surface. Thus, the PA signal ceases to change significantly as β changes and this marks the onset of *saturation*. For higher values of β, *e.g.*, β_4, the distribution is pinned against the illuminated surface and the PA signal does not vary with further increases in β. This is the condition for full saturation and occurs for opaque materials such as carbon black. Thus, whenever $\beta < a_s$, the PA signal will be proportional to β and the electronic absorption spectrum will be measured. When $\beta \gtrsim a_s$, the PA signal will be insensitive to β and remain constant until β decreases. However, when $\beta \gtrsim a_s$ (*i.e.*, near the saturation region), the absorption spectrum may still be obtained by exploiting the frequency dependence of a_s in equation (1). By using higher chopping frequencies ω, a_s may be increased to a value greater than β and the true optical absorption spectrum can be obtained by the PA effect. This beneficial effect is counteracted by the fact that the PA signal decreases in magnitude as ω increases and this limits the high frequencies one may use. The frequency dependence of the magnitude of the PA signal may also be used as a diagnostic tool to indicate when saturation is occurring in opaque samples ($\beta d \gg 1$, where d is the depth of the sample). When one is in the saturation region, the magnitude of the PA signal varies as ω^{-1}. At higher frequencies, or when $\beta < a_s$ and saturation is not occurring, the PA signal varies as $\omega^{-3/2}$ at a given wavelength.

An order of magnitude estimate of the value of β which may lead to saturation can be obtained from the thermal diffusivity, α_s. For most materials and liquids, α_s varies from 10^0 to 10^{-3} cm^2/s, and a_s (at $\omega/2\pi = 100$ Hz) from *ca.* 10 to 500 cm^{-1}, respectively. For $\omega/2\pi = 10^3$ Hz, a_s varies between *ca.* 50 and 2000 cm^{-1}. Thus, any value of $\beta \gtrsim 5000\ cm^{-1}$ may lead to saturation for chopping frequencies of *ca.* 10^3 Hz. This order of magnitude of β as well as the frequency dependences of the PA signal mentioned above have been confirmed experimentally[5].

These results are summarized in Figure 11 which shows hypothetical optical absorption and PA spectra. Saturation is assumed not to occur for $\beta < 10^4\ cm^{-1}$. Thus, in the wave-

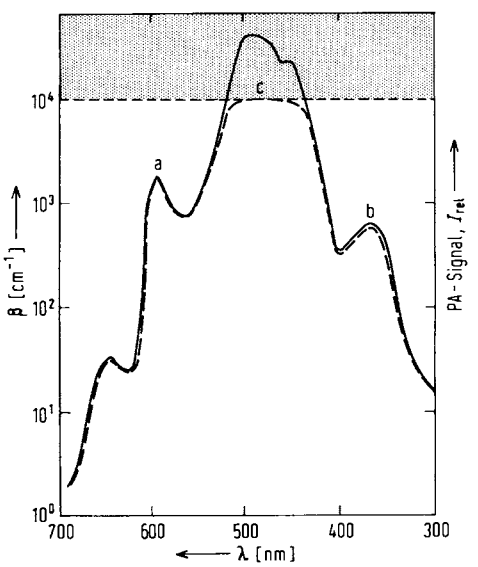


Fig. 11. Comparison of optical absorption (—) and PA (---) spectra of a hypothetical sample, showing the effect of signal saturation. Saturation occurs in the gray zone.

length region where $\beta < 10^4\ cm^{-1}$, the PA spectrum will yield the true optical absorption spectrum. Also, the frequency dependence of the PA signal will be given by $\omega^{-3/2}$ at any wavelength in the region, such as at points a and b. In the wavelength region where $\beta > 10^4\ cm^{-1}$, saturation will occur and the true optical absorption peak height will not be observed in the PA spectrum. The frequency dependence of the PA signal in this range (*e.g.*, at point c) will be given by ω^{-1}. Thus, PAS always gives the *location* of the absorption peaks, but both the absolute and the relative peak heights may not be interpretable in terms of conventional spectroscopic theories.

6. Future Applications of PAS

In the near future, it is quite likely that PAS will become a common and useful analytical tool in many scientific laboratories. Its ease of use and versatility can only increase its areas of application. Examples of some new areas are: 1) low temperature studies of organic and inorganic compounds—modification of a PA cell for low temperature work should be quite straightforward; 2) single crystal studies, using polarized light, of strongly colored materials which could not be readily examined by conventional optical techniques; 3) the use of transform techniques, *e.g.*, the Hadamard transform to improve the signal to noise ratio when the source intensity becomes weak as in the near IR; 4) in the field of catalysis, the characterization of heterogeneous metal oxides and oxide mixtures may prove to be an important application. Similarly, PAS may prove advantageous in the monitoring of surface reactions of metallic catalysts such as platinum and platinum-rhodium combinations which are used in automotive exhaust systems and hydrogenation and hydroformylation reactions; and 5) the exploitation of the phase dependence of the PA signal. This last area appears to be one of the more exciting facets of PAS and could provide an opportunity to obtain more quantitative information from the PA effect. At the present time, typical PA spectrometers measure only half of the information content of the signal (*i.e.*, the amplitude portion). The phase dependence of the PA signal arises from two sources: (a) the lifetime of the excited state and (b) the time it takes for the heat distribution to thermally diffuse to the sample-air interface. If one could prepare a series of samples with approximately the same thermal decay rates, then by measuring the shift in phase of a particular absorption band in the series, information concerning excited state lifetimes and photo- and thermochemical rates and processes could be obtained. Such measurements have already been carried out successfully on gaseous samples[13]. Similarly, by examining the in-phase and out-of-phase (90°) spectrum of a given sample, one can obtain information about the gross macroscopic structure of the sample. This type of measurement has already been done by *Kirkbright*[6] on samples of spinach leaf. He was able to demonstrate the existence of the layered structure of the leaf (*i.e.*, the waxy cuticle plus leaf interior) from such phase measurements. The phase dependence of the PA signal is also an area where additional theoretical effort is needed[14].

In summary, PAS appears quite likely to become a valuable analytical tool. New uses for the technique in various scientific fields are emerging at a rapid rate. In particular, the fields of chemistry, geology, biology, and medicine appear to be the most promising areas for use of PAS in the future.

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^{17}O-NMR Spectroscopy as a Structural Probe

By Walter G. Klemperer[*]

^{17}O-NMR spectroscopy has found limited application as a structural probe due to the experimental problems associated with a quadrupolar nucleus having low natural abundance. A survey of data obtained from systematic studies of structurally related compounds shows, however, that large chemical shift differences are usually obtained for structurally nonequivalent nuclei, and that characteristic chemical shift values are observed for specific chemical environments. The present day availability of ^{17}O enriched materials and Fourier transform NMR instrumentation should allow extensive application of the ^{17}O-NMR technique to structural problems in the immediate future.

1. Introduction

Oxygen, the earth's most abundant chemical element, forms compounds with all the elements except helium, neon and argon. The structure of oxygen-containing compounds is consequently a subject of widespread significance. Since the first observation of ^{17}O nuclear magnetic resonance signals in 1951[1], numerous applications of the technique have been reported. Compared to ^{1}H-, ^{13}C-, ^{19}F-, ^{31}P-, and ^{11}B-NMR, however, ^{17}O-NMR has received little attention as a structural probe. This neglect is not surprising, since ^{17}O has both a low natural abundance and an appreciable electric quadrupole moment, rendering it difficult to observe *via* NMR spectroscopy. Nonetheless, recent advances in NMR instrumentation and an increased availability of ^{17}O enriched materials have alleviated these difficulties, promising renewed interest in the ^{17}O-NMR technique.

This review is concerned with demonstrating the largely unexploited power of ^{17}O-NMR spectroscopy as a structural probe. First, the potential of the technique is discussed in terms of the physical properties of the ^{17}O nucleus. A review of reported ^{17}O-NMR chemical shifts and their sensitivity to structural environment follows. Finally, a brief attempt is made to define unexplored areas where ^{17}O-NMR may provide structural information which is difficult or impossible to obtain using other techniques.

2. Scope and Limitations of the Technique

Of the naturally occurring oxygen isotopes, only ^{17}O possesses nuclear spin ($I = 5/2$)[1,2]. Due to its electric quadrupole moment ($Q = -2.6 \times 10^{-26}$ cm^2)[3,4] and its low natural abundance (0.037 %)[5], the ^{17}O nucleus is one of the more difficult nuclei to observe by NMR spectroscopy. These two properties of the isotope, however, are compensated by the large chemical shifts observed for ^{17}O, which aid in the resolution of quadrupole broadened resonances, and the reactivity of oxygen, which simplifies the synthesis of isotopically enriched compounds.

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2.1. Quadrupolar Broadening

For diamagnetic systems in the absence of rapid site exchange processes, the linewidths of ^{17}O resonances observed in solution are usually limited by quadrupole relaxation rates. The quadrupole relaxation time, T_1, is a function of the electric field gradient q and the asymmetry parameter η at the nuclear site as well as the rotational correlation time τ_c for the molecule as a whole[6]:

$$\frac{1}{T_1} = \frac{3}{125}\left(1 + \frac{\eta^2}{3}\right)\left(\frac{e^2 Q q}{\hbar}\right)^2 \tau_c \qquad \text{(a)}$$

Equation (a) holds under conditions where isotropic molecular tumbling is rapid on the NMR time scale ($\tau_c \ll \omega_0^{-1}$, where ω_0 is the nuclear larmor frequency). Since η, Q and q are constants for a given oxygen site within a molecule, T_1 may be increased to obtain line narrowing only by reducing τ_c, *i.e.* by causing the molecule under study to tumble more rapidly in solution. For a spherical molecule in a continuous medium, the Stokes-Einstein-Debye equation[7] relates τ_c to temperature T, solution viscosity η, and the molecular radius a:

$$\tau_c = \frac{4\pi\eta a^3}{3kT} \qquad \text{(b)}$$

Although equation (b) has limited quantitative significance for real systems, it may in general be used qualitatively to relate sample conditions to observed linewidths. First, raising solution temperature lowers τ_c and leads to line narrowing. Second, line narrowing results from a lowering of solution viscosity, which may be achieved by using a solvent having low viscosity, using low concentration of sample in the solvent, and raising solution temperature. Finally, equation (b) indicates that increased molecular radius implies greater linewidths, with the general consequence that smaller molecules will yield better resolved spectra.

In summary, ^{17}O-NMR linewidths may be minimized to yield optimum spectral resolution by observing resonances at elevated temperature and low sample concentration in a solvent having low viscosity. Note that line narrowing also improves the signal-to-noise ratio for a given integrated signal intensity.

2.2. Sensitivity

The low natural abundance of ^{17}O limits observation of its NMR signals in unenriched samples to pure liquids or concentrated solutions. When dealing with large molecules, the use of pure liquids or concentrated solutions implies high viscosity, which in turn implies broad resonances and limited resolution (see Section 2.1). Consequently, large molecules must be observed in dilute solutions, leading to a sensitivity problem. This problem may be overcome by ^{17}O enrichment and/or extensive signal accumulation using Fourier transform NMR (FT-NMR) techniques. The precise balance between degree of enrichment and amount of signal accumulation will depend upon the relative time and cost factors involved in each alternative.

A brief discussion of the FT-NMR technique[8, 9] is warranted in light of the widespread availability of FT-NMR instrumentation and the improved signal-to-noise ratios which this technique yields relative to continuous wave (CW) techniques. The rapid quadrupole relaxation of ^{17}O nuclei rules out the use of long delay times between the end of each RF pulse and the beginning of data collection without significant loss of sensitivity. As a result, incomplete spectrometer recovery following the RF pulse ("pulse breakthrough") leads to baseline distortions in transformed spectra. Although this problem may be overcome under certain circumstances through judicious selection of delay times and software manipulation[10, 11], a general instrumental solution is lacking at present. Whenever possible, samples should not be observed in dilute aqueous solutions where the strong solvent resonance aggravates the above mentioned problems, and efforts should be made to increase T_1 (see Section 2.1), thus allowing longer delay times to be used.

3. Applications

In this review, no attempt will be made to provide an exhaustive tabulation of known ^{17}O-NMR chemical shifts. Instead, attention will be focussed on classes of compounds where sufficient data are available such that structure features may be correlated with chemical shift values. Analysis will proceed on an empirical basis, the objectives being the generation, interpretation, and application of ^{17}O-NMR chemical shift scales. As a result, calculations of chemical shift values, correlations of ^{17}O-NMR chemical shifts with ^{13}C- and ^{14}N-NMR chemical shifts, and correlations of ^{17}O-NMR chemical shifts with UV and IR absorption frequencies will not be reviewed. All chemical shifts $\delta(^{17}O)$ quoted below are in parts per million relative to pure H_2O, with positive values indicating downfield shifts. Due to the large linewidths of most ^{17}O resonances, errors of about 3 ppm are usually associated with chemical shift values. Many chemical shifts reported in the early literature are inaccurate, and values quoted in this review have been selected after careful comparison of all available data.

3.1. Oxygen Bonded to Main Group Elements

Systematic ^{17}O-NMR studies of compounds containing oxygen bonded to main group elements have dealt largely with group 4b—7b compounds due to their thermodynamic and kinetic stability. In this section, only those compounds will be considered which contain oxygen bonded solely to main group elements. When an oxygen is bonded to two or more atoms belonging to different groups, its chemical shift value will be discussed under the group of the atom which has the highest group number.

3.1.1. Group 4b

The vast majority of ^{17}O-NMR studies on group 4b compounds have treated compounds containing oxygen bonded only to carbon and/or hydrogen. A chemical shift scale which summarizes available data is shown in Figure 1. Chemical shifts not included in Figure 1 are listed in Table 1. All measurements were obtained from either pure liquids or solutions where solvent effects are negligible.

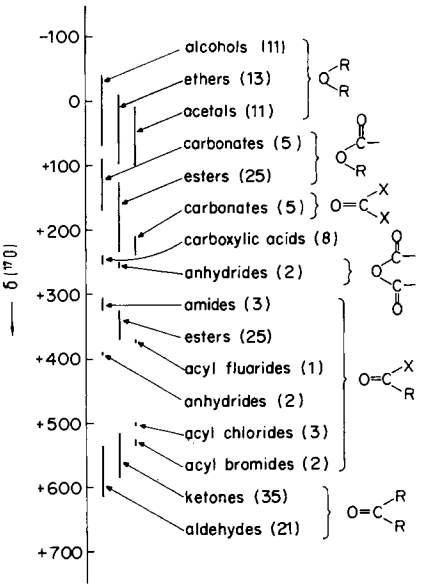
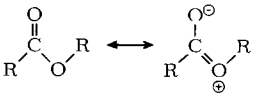


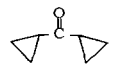
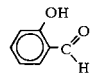
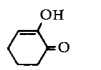
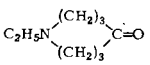
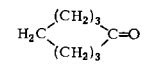
Fig. 1. An ^{17}O-NMR chemical shift scale for carbon compounds. The parenthesized numbers indicate the number of chemical shifts which have been measured for each type of compound. In grouping together classes of compounds on the far right, R represents a hydrogen atom or a carbon atom bonded to carbons, hydrogens, halogens and/or oxygens in the form of alkoxy or aryloxy substituents, and X represents an amino, alkoxy, aryloxy or halide substituent. To simplify the chart, chlorocarbonates have been classified as esters, and orthoesters and ketals have been classified as acetals (all data were obtained from references [11, 12, 15—17, 19 and 20]).

Examination of Figure 1 reveals a clear correlation between C—O π bond order and downfield chemical shift[12, 21]. The chemical shifts for bridging oxygens undergo downfield displacements when R substituents (see Figure 1) are replaced by π accepting acyl substituents which introduce π character into the bridging oxygen's C—O bond:

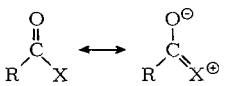


Thus bridging oxygen resonances in carbonates and esters appear downfield relative to the corresponding resonances in alcohols, ethers, and acetals. An even greater downfield

Table 1. ^{17}O-NMR chemical shifts for carbon compounds.

Compound		δ(^{17}O) Bridging	δ(^{17}O) Terminal	Ref.
(1)		+241		[12]
(2)		+237	+530	[12]
(3)	CO_3^{2-}		+192	[13]
(4)			+472	[14]
(5)			+498	[15]
(6)		+ 52	+495	[16]
(7)			+516	[17]
(8)			+576	[17]
(9)	$Mn_2(CO)_{10}$		+355	[18]
(10)	$Ni(CO)_4$		+362	[18]
(11)	$Co(NO)(CO)_3$		+377	[18]
(12)	$Fe(CO)_5$		+388	[18]
(13)	$Fe(NO)_2(CO)_2$		+418	[18]

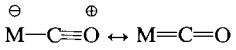
shift is observed for anhydrides, where bridging oxygens are bonded to two π acceptors. Similar effects control chemical shift values for terminal oxygen resonances. Carbonyl chemical shifts are displaced upfield by π donor substituents which weaken the C—O π bond:



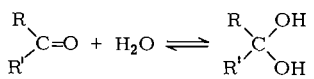
This effect is cumulative, and when two π donors are introduced, as in carbonates, terminal oxygen resonances are substantially displaced upfield and appear in the region characteristic of bridging oxygens in esters and anhydrides. The substituent effects which control chemical shift values within the ranges delineated in Figure 1 have been discussed in detail by several workers[12, 15, 19, 20].

It is instructive to consider the chemical shifts listed in Table 1 within the context of the chemical shift scale shown in Figure 1. In the furan heterocycle, π delocalization leads to a large downfield shift of the bridging oxygen resonance relative to normal ether resonances [see compounds *(1)* and *(2)*]. If chemical shifts are assumed to depend linearly on π bond order, the chemical shift of about +600 ppm for aliphatic aldehydes (π bond order of about 1) relative to water (π bond order of 0) implies a chemical shift of about +200 ppm for CO_3^{2-} (π bond order of 1/3). The observed chemical shift for CO_3^{2-}, +192 ppm, is in agreement with this crude prediction, further supporting the general correlation between π bond order and chemical shift discussed above. The carbonyl resonance in compound *(4)* is upfield from the characteristic range for ketones, reflecting a weakening of the C—O π bond by the two cyclopropyl substituents. In compounds *(5)* and *(6)*, the carbonyl resonances are shifted upfield by hydrogen bonding interactions. These interactions may also be observed as solvent effects. The acetone oxygen resonance, for example, can be displaced up to 50 ppm upfield by protic solvents[15, 22]. Transannular interactions in cyclic ketones have been monitored by ^{17}O-NMR in an analogous manner[17]. In compound *(7)*, transannular interaction of the amine nitrogen with the carbonyl group shifts the ketone resonance 60 ppm upfield relative to the ketone resonance in *(8)* where the amine nitrogen is absent.

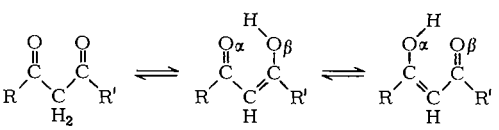
For the sake of completeness, chemical shifts for several transition metal carbonyls have been included in Table 1. If a valence bond model is assumed, the variations in chemical shift observed for compounds *(9)*—*(13)* may be interpreted as reflecting relative magnitudes of π backbonding interactions:



Several studies have utilized ^{17}O-NMR to probe equilibria between organic species. When aldehydes or ketones enter aqueous solution, an equilibrium is established between carbonyl and *gem*-diol structures:



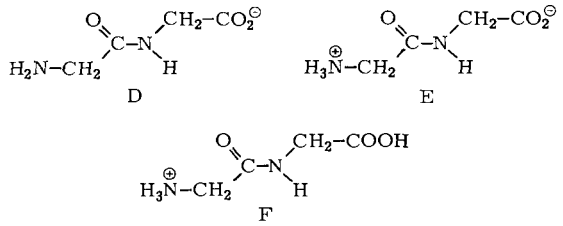
Since carbonyl and alcohol resonances are separated by approximately 550 ppm, this equilibrium can be monitored by ^{17}O-NMR[23]. The equilibrium between the keto and enol forms of β-diketones has been investigated in a similar fashion[16]:



A B C

For symmetric diketones (R = R'), only one resonance is observed for the enol forms B and C since tautomerism is rapid on the NMR time scale. When R ≠ R', two resonances, corresponding to the nonequivalent α and β oxygens, are observed for the enol forms. The chemical shift values for the O_α and O_β resonances may then be used to calculate the relative concentrations of B and C.

Recently, *Irving* and *Lapidot*[24] reported the pH dependence of ^{17}O-NMR chemical shifts of aqueous glycylglycine. Glycylglycine exists in anionic, zwitterionic, and cationic forms under basic, neutral, and acidic conditions, respectively:



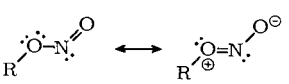
D E F

The carboxylate oxygen resonance behaves in a typical[22] fashion, shifting 19 ppm upfield upon protonation of D or E. The amide oxygen resonance, however, behaves in a more unusual fashion, shifting 6 ppm upfield when the carboxy group of F is deprotonated and shifting a further 16 ppm upfield when the ammonium nitrogen is deprotonated. These shifts presumably reflect the influence which neighboring charges have on the character of the C—O and C—N bonds. Formation of the negative carboxylate group enhances C—N π bonding by stabilizing the resulting positive charge on nitrogen. This enhanced C—N π bonding diminishes C—O π bonding, resulting in an upfield shift of the amide oxygen resonance. Deprotonation of the ammonium group removes positive charge from the vicinity of the carbonyl carbon, allowing the C—O bond to become more polar. The C—O π bond is thus weakened, shifting the amide oxygen resonance upfield.

^{17}O-NMR spectroscopy has also been used to study the kinetics of oxygen exchange reactions between carbonyl compounds and water. When rates are slow, oxygen exchange may be measured by dissolving ^{17}O enriched compound in unenriched water and following the decay of the ^{17}O-NMR signal intensity as a function of time. Alternatively, unenriched compound may be dissolved in enriched water, and the increase in signal intensity monitored. A number of β-diketones and simple ketones have been investigated using these techniques[17, 25–27]. When oxygen exchange rates are rapid, ^{17}O resonances are broadened and the degree of broadening may be related to the exchange rate. Oxygen exchange between acetaldehyde and water under acidic conditions has been studied in this fashion[28].

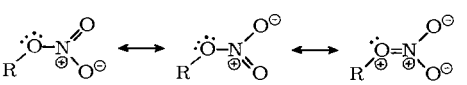
3.1.2. Group 5b

Chemical shift data for representative nitrogen compounds are summarized in Table 2. As in carbon compounds, chemical shift values are determined largely by π bonding effects[12, 15, 29, 32, 37]. Bridging oxygen resonances are observed furthest downfield in nitrites *(28)*, where π bonding is appreciable:



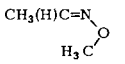
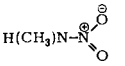
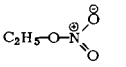
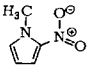
(28)

A lesser but nonetheless significant effect is observed for bridging oxygens in nitrates *(19)*:



(19)

Table 2. ^{17}O-NMR chemical shifts for nitrogen compounds.

Compound		δ(^{17}O) Bridging	Dioxo terminal	Monoxo terminal	Ref.
(14)		+ 35			[12]
(15)		+157			[12]
(16)			+420		[29]
(17)			+425		[29]
(18)			+443		[30]
(19)		+340	+470		[31]
(20)			+519		[32]
(21)			+535		[32]
(22)	 [a]		+560 to +620		[12, 15, 33–36]
(23)			+670		[13]
(24)		+350		+475	[12]
(25)		+460			[12]
(26)	$(CH_3)_2N-N^{=O}$			+660	[29]
(27)	$(C_2H_5)_2N-N^{=O}$			+683	[12]
(28)	$R-O-N^{=O}$ [b]	+420 to +513		+790 to +838	[12, 29]
(17)	$O_2N-N^{=O}$			+885	[29]
(29)	$Cl-N^{=O}$			+915	[29]

[a] R = alkyl or phenyl; [b] R = alkyl.

Compounds *(24)* and *(25)* provide further examples of π delocalization effects.

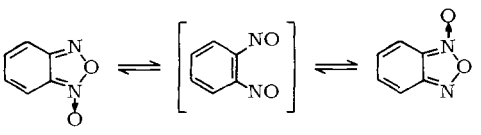
Within the class of compounds X—NO_2 which contain dioxo terminal oxygens, chemical shifts are displaced upfield as N—O π bonding is weakened by X—N π bonding. The considerable degree of N—N π bonding in *(16)* and *(17)* is reflected in chemical shifts which lie close to the +410 ppm[19] value observed for NO_3^-. The greatest downfield shifts are observed for the terminal oxygens in compounds containing the —N=O moiety. Here again, resonances are shifted upfield as X—N π bonding increases in X—NO. Further substituent effects in nitro compounds and nitrites have been discussed in detail, and most trends can be interpreted in terms of π delocalization and hydrogen bonding effects[12, 15, 29, 32, 34, 35, 37].

^{17}O-NMR spectroscopy has been used to study charge distributions in deprotonated nitro compounds[30, 33, 36–38]. When nitromethane is deprotonated, for example, its ^{17}O-NMR chemical shift is displaced 405 ppm upfield as a consequence of extensive negative charge delocalization onto oxygen:



In the case of dinitro- and trinitromethane, deprotonation leads to upfield displacements of 180 and about 75 ppm, respectively. These smaller displacements are a result of charge delocalization over a greater number of nitro groups. Similar chemical shift changes are observed upon deprotonation of other nitroalkanes, nitramines, and nitropyrroles.

Dynamic processes in nitrogen compounds have also been examined. At room temperature, benzofurazan oxide displays two ^{17}O resonances corresponding to its terminal and bridging oxygens. As the sample temperature is raised, however, these resonances broaden and coalesce into a single resonance. This observation is consistent with fluxional behavior[39][*]:



^{17}O-NMR chemical shifts have been measured for a number of compounds containing phosphorus-oxygen bonds[12, 13, 15, 40], but since these chemical shifts lie in a rather narrow range, systematic analysis is difficult. In the case of hypophosphorous, phosphorous, and phosphoric acids and esters, for example, all reported resonances lie between +38 and +102 ppm. Greater variations in chemical shift are observed within the family of compounds OPX_nCl_{3-n} (Table 3). Although the effects of various X substituents in $OPCl_2X$ parallel the effects of the same substituents on chemical shifts in the RCOX family (Fig. 1), these trends are no longer maintained in the further substituted compounds $OPClX_2$ and OPX_3.

In contrast with the carbon and nitrogen compounds discussed thus far, coupling constants have been measured in several phosphorus compounds. ^{17}O—^{31}P coupling constants ranging from 90 to 308 Hz have been reported[12, 15, 40], and an attempt has been made to correlate coupling constants with phosphorous-oxygen bond strengths[40]. In view of the limited number of data available, however, this correlation must be viewed as tentative.

Table 3. ^{17}O-NMR chemical shifts for related phosphorus compounds [a].

	X=Br	X=F	X=OCH$_3$	X=N(CH$_3$)$_2$
$OPCl_2X$	+232	+177	+167	+150
	(+17)	(−38)	(−48)	(−65)
$OPClX_2$	+245	+127	+124	+125
	(+30)	(−88)	(−91)	(−90)
OPX_3	+259	+ 66	+ 68	+ 73
	(+44)	(−149)	(−147)	(−142)

[a] The numbers in parentheses are chemical shifts in ppm relative to $OPCl_3$, which has a +215 ppm chemical shift relative to H_2O. All data are from ref. [40], except the $OP(OCH_3)_3$ shift which is from ref. [15].

[*] This long known behavior has already been investigated ^{1}H- and ^{13}C-NMR spectroscopically.

3.1.3. Group 6b

Although it is difficult to rationalize the large chemical shifts found for compounds containing oxygen-oxygen bonds [see Table 4, compounds *(30)* to *(34)*], the ability of ^{17}O-NMR spectroscopy to unambiguously distinguish between nonequivalent oxygens has found application in mechanistic studies[42, 43]. *Solomon et al.*[42], for example, studied the CsF catalyzed reaction of OF_2 with COF_2 to form CF_3OOOCF_3 by reacting ^{17}O enriched OF_2 with unenriched COF_2 and also reacting unenriched OF_2 with enriched COF_2. In the first case, the CF_3OOOCF_3 product displayed only the central oxygen resonance, whereas only the peripheral oxygen resonance was observed in the second case. These results support the following mechanism:

$$F_2CO + CsF \rightarrow Cs^{\oplus}F_3CO^{\ominus}$$
$$F_3CO^{\ominus} + OF_2 \rightarrow F_3COOF + F^{\ominus}$$
$$F_3CO^{\ominus} + F_3COOF \rightarrow F_3COOOCF_3 + F^{\ominus}$$

Table 4. ^{17}O-NMR chemical shifts for oxygen and sulfur compounds.

	Compound	δ(^{17}O)	Ref.
(30)	O_3	+1032 [a], +1598 [b]	[41]
(31)	CF_3OOOCF_3	+ 321 [c], + 479 [d]	[42]
(32)	$(CH_3)_3COOC(CH_3)_3$	+ 269	[12]
(33)	$(CH_3)_3COOH$	+ 260	[12]
(34)	H_2O_2 [f]	+ 187	[13]
(35)	SO_2Cl_2	+ 304	[13]
(36)	$S_2O_3^{2-}$	+ 228	[44]
(37)	$C_6H_5SO_2Cl$	+ 221	[12]
(38)	FSO_2OSO_2F	+ 238 [a], +167 [b, e]	[43]
(39)	SO_4^{2-}	+ 167	[44]
(40)	$SO_2(OCH_3)_2$	+ 102 [a], +150 [b]	[12]
(41)	SO_2F_2	+ 148 [e]	[43]
(42)	H_2SO_4	+ 140	[12]
(43)	SO_2	+ 513	[13]
(44)	$SOCl_2$	+ 292	[13]
(45)	SO_3^{2-}	+ 235	[45]
(46)	$OS(OCH_3)_2$	+ 115 [a], +176 [b]	[12]
(47)	$OS(CH_3)_2$	+ 13	[12]
(48)	$CH_3OSSOCH_3$	+ 14	[12]
(49)	$S(OCH_3)_2$	+ 12	[12]

[a] Bridging oxygen. [b] Terminal oxygen. [c] Peripheral oxygen. [d] Central oxygen. [e] Triplet. [f] 30% aqueous solution.

Far more chemical shift data are available for sulfur containing compounds [see Table 4, compounds *(35)* to *(49)*]. Within the family of four coordinate S^{VI} compounds *(35)* to *(42)*, terminal oxygen chemical shifts may be rationalized in terms of π bonding effects. The resonance for SO_4^{2-} *(39)*, however, is anomalous in this respect, lying slightly downfield from the $SO_2(OCH_3)_2$ *(40)* and SO_2F_2 *(41)* resonances. Analogous trends are apparent in the remaining terminal oxygen resonances [compounds *(43)* to *(47)*]. Here the resonance for dimethyl sulfoxide *(47)* provides the most striking anomaly, lying 163 ppm upfield from the terminal oxygen

resonance for dimethyl sulfite *(46)*. A possible explanation for this anomaly is provided by *Coulson*'s analysis for d orbital participation in main group compounds[46]. Sulfur 3d orbitals are sufficiently contracted to participate significantly in π bond formation only when the formal charge on sulfur is high. In dimethyl sulfite, the three oxygen substituents raise the formal charge on sulfur sufficiently, whereas the single electronegative substituent in dimethyl sulfoxide is apparently unable to. The bridging oxygen chemical shifts in compounds *(38)*, *(40)*, *(46)*, *(48)*, and *(49)* are ordered approximately as expected: π acceptor substituents lead to downfield shifts.

^{17}O-NMR spectroscopy has been applied to stereochemical problems in sulfur chemistry by several workers. *Jackson* and *Taube*[45] attempted to characterize the complex equilibria present in the SO_2/H_2O system, but the low level of ^{17}O enrichment available was insufficient to allow complete, unambiguous interpretation. *Solomon et al.*[43], investigated the reaction of SO_2 with O_2F_2 using ^{17}O-NMR techniques. The oxygens in SO_2F_2 product were shown to originate from the SO_2 not the O_2F_2, and the oxygens in FSO_2OSO_2F product were shown to originate from both O_2F_2 and SO_2, randomized in the product. Further applications will be discussed in the next section.

3.1.4. Group 7b

As was the case for compounds containing oxygen-oxygen bonds (see Section 3.1.3), compounds containing oxygen-fluorine bonds display large downfield chemical shifts [see Table 5, compounds *(50)* to *(52)*]. Since the observation of ^{17}O—

Table 5. ^{17}O-NMR chemical shifts for fluorine and chlorine compounds.

	Compound	δ(^{17}O)	Ref.
(50)	OF_2	+830 [a]	[41]
(51)	FSO_2OOF	+669 [b, e], +365 [c], +152 [d, e]	[43]
(52)	O_2F_2	+647 [a]	[47]
(53)	ClO_2^+	+784	[48]
(54)	ClO_2F	+384	[48]
(55)	$ClOF_3$	+311	[48]
(56)	ClO_3F	+302 [f]	[48]
(57)	$HClO_4$	+290 [g]	[48]
(58)	ClO_4^-	+290 [g]	[49]
(59)	ClO_3^-	+290	[49]
(60)	$(CH_3)_3COCl$	+ 79	[12]

[a] Triplet; [b] O—F; [c] O—S; [d] O=S; [e] Doublet; [f] Unresolved quadruplet; [g] Quadruplet.

^{19}F coupling aids in assigning resonances, ^{17}O-NMR spectroscopy has proved to be a useful structural probe for oxygen-fluorine compounds. Detailed studies of the "O_3F_2" system[41,47], which yields resonances at +647, +971, and +1512 ppm, implicated mixtures of O_2F_2 *(52)* and "$(O_2F)_n$" as opposed to discrete O_3F_2 species. Although the "$(O_2F)_n$" species could not be assigned a definite structure, the NMR data were interpreted in terms of a dimeric FO_4F structure. ^{17}O-NMR spectroscopy was also used in labeling experiments which demonstrate that O_2F_2 reacts with SO_2 to form FSO_2OOF *(51)* *via* an OOF intermediate derived from the O_2F_2 reactant[43].

The ^{17}O-NMR data available for chlorine compounds [Table 5, compounds *(53)* to *(60)*] illustrate two interesting effects. First, the fact that $HClO_4$ *(57)* in acidic aqueous solution and ClO_4^- *(58)* in basic aqueous solution display identical chemical shifts reflects the nonbasic character of the perchlorate ion. Second, the observation of ^{17}O—^{35}Cl spin-spin splitting in ClO_4^- but not in ClO_3^- illustrates the factors which usually prevent the measurement of coupling constants between ^{17}O and quadrupolar nuclei, here ^{35}Cl. In ClO_4^-, the ^{35}Cl nucleus is in a tetrahedral environment where the electric field gradient is zero and quadrupolar relaxation is inhibited. Thus the lifetimes of the individual ^{35}Cl spin states are long enough to produce splitting of the ^{17}O resonance. In ClO_3^-, however, the C_{3v} ^{35}Cl environment allows for rapid quadrupolar relaxation of the ^{35}Cl nucleus, and the lifetimes of the individual ^{35}Cl spin states are too short to generate multiplet structure in the ^{17}O-NMR spectrum.

3.2. Oxygen Bonded to Transition Elements

^{17}O-NMR spectroscopy has been employed frequently to determine transition metal ion hydration numbers and water exchange rates, but the technique has received relatively little application in structural studies. Most stereochemical studies have dealt with polynuclear, anionic oxo complexes (polyoxoanions) of the early transition elements in their highest oxidation states. In spite of their structural complexity, these polyoxoanions often yield well resolved ^{17}O-NMR spectra since large chemical shifts are observed and samples often may be observed at elevated temperatures in nonviscous solvents. Most polyoxoanions are prepared in aqueous solution, and ^{17}O enrichment is therefore easily obtained.

3.2.1. Group 5a

Of the fully oxidized group 5a metals, only vanadium forms tetrahedral oxoanions in aqueous solution. The vanadate ion, VO_4^{3-}, displays a ^{17}O-NMR multiplet at +568 ppm with $J(^{17}O—^{51}V) = 61.6$ Hz[50]. At about pH = 13, an additional symmetric doublet appears at +700 ppm which has been assigned to the ion $O_3VOVO_3^{4-}$[50].

Polyvanadate equilibria in acidic aqueous solution have also been studied. At pH 5.5—6.0, $V_{10}O_{28}^{6-}$ is the predominant species, in equilibrium with smaller amounts of metavanadate, $V_4O_{12}^{4-}$. At lower pH, the metavanadate concentration decreases, and the $V_{10}O_{28}^{6-}$ anion becomes protonated. These equilibria have been studied using ^{17}O-NMR spectroscopy[51]. Interestingly, the pH dependence of ^{17}O-NMR chemical shift values for $V_{10}O_{28}^{6-}$ (Table 6) reveals the location of protonation sites in the anion. Since protonation of an oxygen weakens its O—V bonds, its chemical shift is displaced upfield. The chemical shifts for unprotonated oxygens shift downfield since their O—V bonds are strengthened in order to maintain approximately constant total bond order at vanadium. Consequently, the observed chemical shift displacements resulting from acidification of aqueous $V_{10}O_{28}^{6-}$ (Table 6) demonstrate that protonation occurs at oxygens O_B and O_C (Fig. 2A).

Time dependent ^{17}O-NMR spectra of unenriched $Na_6V_{10}O_{28}\cdot 18H_2O$ dissolved in ^{17}O enriched water yield information regarding the mechanism of oxygen exchange between $V_{10}O_{28}^{6-}$ and water[51]. Initially, only a metavanadate resonance is observed at +925 ppm, but as the system approaches equilibrium, the $V_{10}O_{28}^{6-}$ resonances appear at equal rates. This result indicates that oxygen exchange in $V_{10}O_{28}^{6-}$ proceeds *via* reversible dissociation to metavanadate.

Table 6. ^{17}O-NMR chemical shifts for selected groups 5a and 6a polyoxoanions.

	Anion	Structure [a]	Ref.	Solvent	δ(^{17}O) [b]	Ref.
(61)	$V_{10}O_{28}^{6-}$	**A**	[55]	H_2O, pH ≈ 6.0	+62 (A), +406 (B), +766 (C), +780 (D), +893 (E), +1143 (F, G)	
				H_2O, pH = 4.5	+72 (A), +378 (B), +759 (C), +803 (D), +904 (E), +1160 (F, G)	[51]
(62)	$Nb_6O_{19}^{8-}$	**B** [c]	[56]	H_2O, pH ≈ 13	+20 (A), +386 (B), +594 (C)	[52]
(63)	$Ta_6O_{19}^{8-}$	**B** [c]	[57]	H_2O, pH = 13	−41 (A), +329 (B), +476 (C)	[52]
(64)	$Mo_6O_{19}^{2-}$	**B**	[58]	$HCON(CH_3)_2$	−32 (A), +559 (B), +927 (C)	[53]
(65)	$Mo_7O_{24}^{6-}$	**C**	[59]	H_2O, pH = 5.5	+123 (A), +338 (B), +400 (C, D), +758 (E), +821 (F to I)	[53]
(66)	β-$Mo_8O_{26}^{4-}$	**D**	[60]	CH_3CN	+56 (A), +296 (B), +425 (C), +743 (D), +866 (E to H), +900 (I)	[54]
(67)	α-$Mo_8O_{26}^{4-}$	**E**	[54,61]	CH_3CN	+396 (A), +495 (B), +755 (C), +866 (D)	[54]

[a] Letter identifies idealized structure shown in Fig. 2; [b] Parenthesized letter is the assignment of the resonance using the labeling scheme given in Fig. 2; [c] Isostructural with $Mo_6O_{19}^{2-}$.

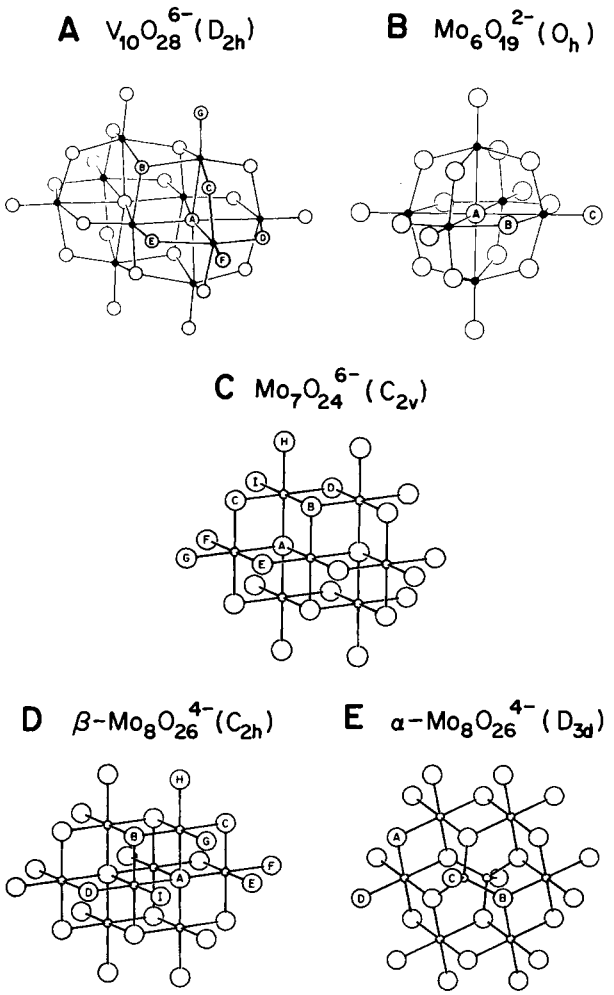


Fig. 2. Idealized structures of some polyoxoanions which indicate the oxygen labeling scheme used in Table 6. The point group symmetry for each idealized structure is indicated in parenthesis. For detailed structures, see the references given in Table 6.

^{17}O-NMR spectroscopy has found little application in polyniobate and polytantalate chemistry. Resonances have been observed (Table 6) for $Nb_6O_{19}^{8-}$ and $Ta_6O_{19}^{8-}$, however, and more extensive studies of these systems should yield results analogous to those obtained in the polyvanadate system.

3.2.2. Group 6a

A large number of ^{17}O-NMR chemical shifts have been reported for group 6a oxoanions and polyoxoanions[13, 44, 45, 50–54, 62, 71]. Since an exhaustive survey of these data is beyond the scope of this review, only selected results will be discussed in detail. Emphasis will be placed on methods for assigning resonances in complex spectra.

Kidd[62] has demonstrated that ^{17}O-NMR chemical shifts for hexavalent chromium compounds are determined largely by metal-oxygen π bond order. A plot of chemical shifts for CrO_2Cl_2 (+1460 ppm), $O_3CrOCrO_3^{2-}$ (+1129 ppm terminal oxygens, +354 ppm bridging oxygen), and CrO_4^{2-} (+835 ppm) *versus* π bond orders derived from simple valence bond formulas shows an approximately linear relationship between π bond order and downfield chemical shifts. Similar trends are observed for hexavalent, four-coordinate molybdates: the MoO_4^{2-} resonance appears at +532 ppm[44, 64], and the terminal and bridging oxygen resonances for $O_3MoOMoO_3^{2-}$ appear at +715 and +248 ppm, respectively[67].

Assignment of resonances for complex polymolybdates and polytungstates containing six coordinate Mo^{VI} and W^{VI} is more difficult. The polymolybdates *(64)* to *(67)* (see Table 6) provide representative examples of the procedures used to analyze complex spectra. The $Mo_6O_{19}^{2-}$ anion *(64)* contains three types of oxygens (see Fig. 2B): Six terminal oxygens with $d_{Mo-O} = 1.68$ Å (O_C), twelve doubly bridging oxygens with $d_{Mo-O} = 1.93$ Å (O_B), and one six-fold bridging oxygen with $d_{Mo-O} = 2.32$ Å (O_A). Assuming π bond order increases as d_{Mo-O} decreases, the three observed resonances may be assigned as in Table 6. This assignment is consistent with the observed intensities and with the very narrow linewidth observed for the sixfold bridging oxygen, which is in an octahedral environment where quadrupolar relaxation has been inhibited.

The $Mo_7O_{24}^{6-}$ anion *(65)*, although it contains nine symmetry nonequivalent types of oxygens, displays only five ^{17}O resonances. Assigning all of the terminal oxygen to the +821 ppm resonance leaves five types of oxygens to be assigned to the four remaining resonances. Assuming that the more metals an oxygen atom bridges, the further upfield its resonance lies, the +123 and +338 ppm resonances are assigned to the fourfold and threefold bridging oxygens respec-

tively. This leaves two resonances at +400 and +758 ppm to be assigned to the three types of doubly bridging oxygens. One type of doubly bridging oxygen (O_E) has an unusually short bond distance ($d_{Mo-O}=1.74$ Å) to the molybdenum which has no terminal oxygens, and the +758 ppm resonance is assigned to this type of oxygen. Although the assignments are consistent with those found in simpler compounds (see below) they cannot account for the approximately equal intensities of the +338 and +400 ppm resonances. This discrepancy may indicate an incorrect assignment.

The resonances for the β-$Mo_8O_{26}^{4-}$ anion *(66)* are assigned in a similar fashion, and the relative intensities implied by these assignments are consistent with the observed intensities. The α-$Mo_8O_{26}^{4-}$ anion provides an additional complexity since it contains both four- and six-coordinate molybdenums. The terminal oxygen resonances are assigned using intensity arguments, and the +396 ppm resonance is assigned to the doubly bridging oxygen bonded to two molybdenums, each of which has two terminal oxygens, by analogy with the previous compounds. This leads to assignment of the +495 ppm resonance to the triply bridging oxygen bonded to the four coordinate molybdenum. Comparison of these assignments with the bond distances in α-$Mo_8O_{26}^{4-}$ yields a self-consistent picture where shorter Mo—O bonds imply larger downfield shifts. Figure 3 summarizes the data which have been obtained for oxygens bonded only to six-coordinate Mo^{VI}. There is no overlap

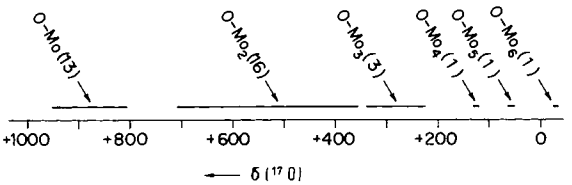


Fig. 3. An ^{17}O-NMR chemical shift scale for oxygens bonded to six-coordinate molybdenums in Mo^{VI} polyoxoanions. Chemical shift ranges are labeled O—Mo_n, where n = the number of molybdenums that type of oxygen is bonded to. The numbers in parenthesis indicate the number of chemical shifts used to determine each range (all data were obtained from references [53, 54, 66, and 70]).

between the chemical shift regions associated with each type of oxygen, but this separation is unlikely to be maintained as further data are measured. Although discussion here has proceeded entirely in terms of polymolybdates, analogous data have been obtained for polytungstates[52, 68–71] where similar factors determine chemical shift values.

Dynamic ^{17}O-NMR techniques were first applied to group 6a compounds in two independent studies of oxygen exchange in the aqueous $CrO_4^{2-}/Cr_2O_7^{2-}$ system. In the first study, by *Figgis et al.*[63], evidence was obtained for nucleophilic attack of CrO_4^{2-} on $Cr_2O_7^{2-}$ leading to substitution at Cr^{VI}:

$$Cr^*O_4^{2-} + O_3CrOCrO_3^{2-} \rightarrow O_3Cr^*OCrO_3^{2-} + CrO_4^{2-}$$

This interpretation must be viewed with skepticism, however, since the investigators incorrectly assumed equal linewidths for the terminal and bridging oxygen resonances in $Cr_2O_7^{2-}$ in the absence of oxygen exchange. *Jackson* and *Taube*[45] independently studied the effect of acidification on the linewidths observed for dichromate and solvent resonances in aqueous $Cr_2O_7^{2-}$, and provided strong evidence for the rapid acid catalyzed equilibrium:

$$Cr_2O_7^{2-} + H_2O \rightleftharpoons 2HCrO_4^-$$

More recently, temperature dependent ^{17}O-NMR spectra for α-$Mo_8O_{26}^{4-}$ (see Fig. 2E) were reported which display differential line broadening consistent with rapid reorientation of the tetrahedral MoO_4^{2-} subunits on the NMR time scale[54]. ^{17}O-NMR spectroscopy has also been applied in the structure determinations of $(C_6H_5As)_2Mo_6O_{24}^{4-}$[65] and $(C_6H_5As)_4Mo_{12}O_{46}^{4-}$[66]. The effects of paramagnetic ions on ^{17}O-NMR chemical shifts have been studied in a series of isostructural polytungstates $M^{n+}W_{10}O_{36}^{(12-n)-}$, where $M^{n+}=Ce^{3+}$, Ce^{4+}, Pr^{3+}, Th^{4+}, and U^{4+}[68, 71]. These results demonstrate the feasibility of observing chemical shifts in paramagnetic polyoxoanions and open up new areas for investigation.

4. Areas for Future Investigation

Within the vast areas of oxygen chemistry yet to be systematically investigated by ^{17}O-NMR spectroscopy, three classes of compounds deserve special consideration. First of all, dioxygen complexes of the transition elements warrant reexamination by ^{17}O-NMR techniques. Despite several attempts[72–75], resonances for $^{17}O_2$ in these complexes have never been detected. The failure to observe resonances in dioxygen complexes has been attributed to line broadening due to slow molecular tumbling[75]. A systematic study of small dioxygen complexes in nonviscous solvents at low concentration and elevated temperature should allow this difficulty to be circumvented. Transition metal organometallic compounds are a second class of compounds which have rarely been examined by ^{17}O-NMR spectroscopy[18]. Chemical shifts for nitrosyl and carbonyl ligands are likely to be quite sensitive to stereochemical environment. Finally, polynuclear oxo compounds and alkoxides are obvious candidates for further ^{17}O-NMR investigations. In view of the successes achieved with polyoxoanions of the groups 5a and 6a metals (see above), analogous studies of other polyoxoanions and alkoxides in general are likely to be fruitful.

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Sodium-23 Nuclear Magnetic Resonance Spectroscopy

By Pierre Laszlo[*]

With the availability of Fourier transform spectrometers, ^{23}Na-NMR spectroscopy has become an important tool. It affords direct insight into solvation and ion pairing phenomena, both in organic and in bio-inorganic systems. Monitoring the chemical shifts and linewidths of ^{23}Na signals gives access to binding constants, reorientational correlation times and the microdynamics of the sodium coordination shell. The binding of other cations can also be studied by ^{23}Na-NMR spectroscopy, in competition experiments.

1. Introduction

Sodium, the 6th most abundant element on our planet, is present in rocks and in oceans, in the upper atmosphere and in many organisms. Sodium is indeed essential to life, as we know it.

Selective permeability[1-3], a vital function of the cellular membrane, occurs together with operation of the physiological sodium-potassium pump[4-11]. The normal cell maintains a sodium-poor and potassium-rich cytoplasm, with respect to its saline environment. These concentration gradients are buttressed by the "burning" of adenosine triphosphate. A mechanism proposed for the sodium expulsion and the potassium entry involves conformational changes in the ATPase molecules present in the cell membranes[12].

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Active transport of sodium and potassium across cellular membranes accompanies such various phenomena as the firing of a nerve[13], muscular contractions[14-17], and the activity of the brain[18], bioluminescence[19], accumulation of amino acids in the cells[20], salt and water transport in kidneys[21].

The four cations of greatest biological importance are Na^+, K^+, Ca^{2+} and Mg^{2+}[1]. There exists a wealth of metallic cations having quasi-identical ionic radii, and very similar chemical properties to K^+, or Ca^{2+}, or Mg^{2+}, which they can readily replace (isomorphous substitution[1]).

Unfortunately, such replaceable cations are simply not available for the sodium cation. To quote *Williams*[1]: "Sodium complexes can be studied directly by NMR using ^{23}Na. Relatively little work has been done in this field as yet. Unfortunately a search of the Periodic Table shows that no other cation is likely to mimic the properties of sodium closely so that a detailed understanding of its biochemistry must depend on an extension of the NMR method and not on isomorphous substitution. Lithium does not replace sodium in a biological system. The differences between the two are exemplified by the use of lithium salts in the treatment of nervous disorders".

^{23}Na-NMR spectroscopy is an extremely convenient and, of course, direct means for studying interactions between Na^+ and organic or bio-molecules. For sodium-23, its natural abundance of 100%, and an intrinsic NMR sensitivity of only a factor of 10 less than that of the proton, make it 525 times more sensitive than carbon-13, extensively used in the study of organometallic, organic and biological molecules. With ^{23}Na-NMR spectroscopy, routine examination of centimolar and even millimolar solutions is possible. For comparison, the physiological concentration of Na^+ in a body fluid such as blood serum is approximately decimolar.

2. Instrumental Techniques

The sodium-23 resonance frequency is 26.452 MHz for a magnetic field $\mathbf{B}_0 = 2.35$ tesla (*i.e.* one at which protons resonate at 100 MHz). The question is whether it is more advantageous to record spectra in the slow sweep [or continuous wave (CW)] mode, or in the Fourier (FT) mode.

The relative gain (FT/CW) achieved with the FT method (see Table 1) can be calculated with the aid of the Ernst and Anderson equation[22].

Table 1. Gain (FT/CW) achieved with a typical acquisition time = 5 T_1, and a spectral window of 6000 Hz (> 250 ppm). The gain was calculated according to the Ernst-Anderson equation [22].

Gain (FT/CW)	Linewidth [Hz]
6.4	15
2.5	100
0.8	1000

The continuous wave method only becomes competitive with linewidths close to 1 kHz. According to our experience, *ca.* 80% of the samples examined have resonance linewidths ranging between 5 and 100 Hz; hence, a FT spectrometer is clearly superior. One operates with 90° pulses having a time duration of about 9 μs, corresponding to an examining field $\mathbf{B}_1 = 24.7$ G[23]. This is equivalent to gaining access to a frequency range of 28 kHz without distortion of the spectrum[24]. The actual spectrum occupies a small fraction of this range.

The resolution is given by the inverse of the acquisition time[23], and is of the order of 1.5 Hz: again this is sufficient, since the narrowest lines observed in practice have a width of about 5 Hz.

The actual time required to obtain useful spectra, with a signal-to-noise ratio above 20, is specified in Table 2.

Table 2. Typical recording times with a "90 MHz" and with a "250 MHz" instrument (corresponding to $\mathbf{B}_0 = 2.12$ and 5.88 tesla, respectively).

Linewidth [Hz]	Sample concentration [mol/l]	Recording times at $\mathbf{B}_0$ = 2.12 tesla	5.88 tesla
10	10^{-2}	0.5 h	1 pass
500	10^{-2}	(impossible at present)	12 h
500	10^{-1}	12 h	2 h

3. The Sodium-23 Chemical Shift

^{23}Na chemical shifts are measured with reference to an external standard: an aqueous solution of sodium chloride enclosed in a capillary[25]. After extrapolating to infinite dilution and correcting for difference in magnetic susceptibility[26] between the capillary and sample tubes, the chemical shifts are accurate to ±0.2 ppm, or with slightly more effort to ±0.05 ppm.

The *usual* range for ^{23}Na chemical shifts is *ca.* 40 ppm, *i.e.* rather small for a heavy nucleus, but in line with the small electrical polarizability of the Na^+ cation. However, this range was greatly extended by *Ceraso* and *Dye*[27,28], who obtained a spectrum containing separate signals for the cryptated sodium cation and the sodium anion (Fig. 1) by co-dissolving metallic sodium and the [2.2.2]cryptand (see Table 3)[29] in an organic solvent[30].

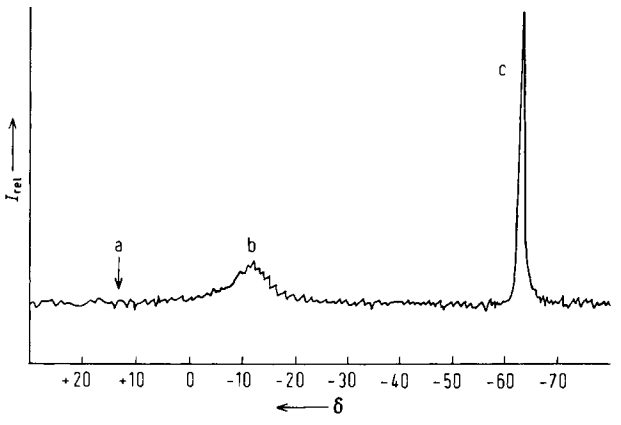


Fig. 1. ^{23}Na-NMR spectrum of a solution of Na[2.2.2]cryptand$^+$Na$^-$ (*ca.* 0.3 M) in ethylamine at 1.4 °C. External standard is saturated aqueous NaCl [27]. a): Na^+ in ethylamine; b) Na[2.2.2]cryptand$^+$; c): Na^-.

The signal of the sodium anion is shifted 63 ppm upfield from the aqueous NaCl reference, is solvent-independent when measured in THF, methylamine and ethylamine and is, within experimental error, the same as that calculated for the gaseous anion[31]: the two electrons in the 3s orbital shield the 2p electrons from the influence of the solvent.

The chemical shift of the sodium cation, on the other hand, is strongly solvent-dependent[32–36]. Thus, *Erlich* and *Popov*[34] found that the ^{23}Na chemical shift can be correlated with the Gutmann donicity (or donor number)[37] of the solvent over a range of almost 20 ppm (see Fig. 2).

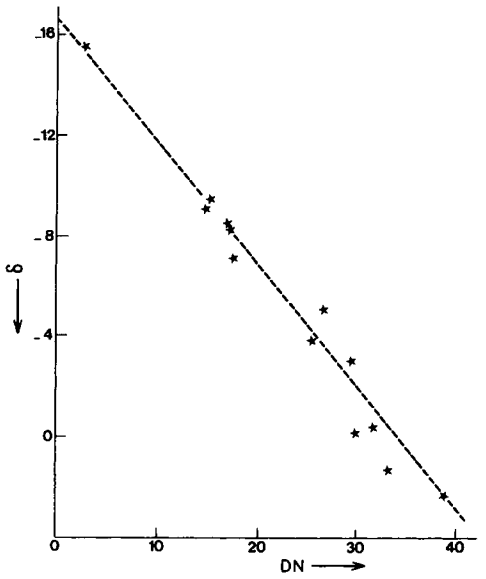


Fig. 2. Chemical shift of Na^+ as a function of the solvent donor number (DN) [37].

Water, a highly-structured solvent, defies this relationship, which, in turn, has been used to determine the donicities of a series of amine solvents[35].

When a gaseous sodium atom ionizes to Na^+, and this is then solvated, the diamagnetic contribution to the chemical shift changes at most by only 10 ppm[31,32,38–40]. In contrast, the paramagnetic term contributes *ca.* 50 ppm to the chemical shift[32,41–43].

This appears paradoxical, since Na^+, like the F^- ion, has no unpaired electrons in p-, d- or f-orbitals, and therefore should have a vanishing paramagnetic contribution to nuclear shielding. In order to account for the observed solvent shifts, it is necessary to assume that electrons are donated by the solvent into a 3p orbital of the sodium atom[32].

This paramagnetic term amounts to *ca.* −270 ppm per unit electronic charge[32], in compliance with the downfield shift observed as the solvent becomes a better electron donor (Fig. 2).

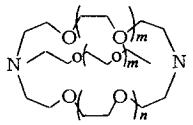
Are electrons truly transferred from the outer s and p orbitals of solvent molecules into the vacant outer p orbitals of the sodium ion?

Very substantial electron transfers of this type are indeed indicated by approximate calculations of the CNDO-INDO type, applied to the interaction of Na^+ with one or several ligand molecules such as water, ammonia, or formaldehyde[44]. More refined calculations of the *ab initio* type, however, reveal only very small degrees of electron transfer: for instance, in the interaction of Na^+ with water molecules, only the first H_2O molecule coordinated to Na^+ by its oxygen atom has a bond that is not purely ionic[45].

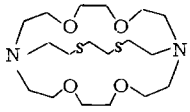
In all the cases which have been carefully investigated, an electrostatic description is adequate for bonding between Na^+ and coordinating dipolar molecules. The ion-dipole is the dominant attractive term. It is counter-balanced by the dipolar repulsion of the ligands[46]. There is no need to postulate substantial amounts of covalency. Thus a full understanding of the sodium-23 chemical shift for the solvated Na^+ cation fails here: the experimental finding of a correlation with the solvent donicity[47,48] (Fig. 2), and the theoretical calculation of the (dominant) paramagnetic term both assume covalent bonding which, to all intents and purposes, is vanishingly small.

Resolution of this problem requires more sophisticated calculations of the ^{23}Na chemical shift for Na^+ in solution, which have yet to be performed. An example will illustrate the relatively poor understanding we actually have of sodium-23 chemical shifts: the spread in chemical shifts for Na^+ encapsulated by various antibiotic ionophores, such as valinomycin, monensin or monactin is almost 25 ppm[49]! Synthetic ionophores of the cryptand type act likewise; depending upon the size of the cavity, *i.e.* upon the precise oxygen-sodium distances, the sodium-23 chemical shift changes by more than 20 ppm[50] (Table 3).

Table 3. Chemical shifts of Na^+ in some cryptates [50].



(1), $m = 0$; $n = 1$
(2), $m = 1$; $n = 0$
(3), $m = n = 1$



(4)

Cryptand	Sodium cryptate	$\delta(^{23}Na)$
(1)	Na[2.1.1]cryptand$^+$	+11.15
(2)	Na[2.2.1]cryptand$^+$	− 4.25
(3)	Na[2.2.2]cryptand$^+$	−11.40
(4)	Na[2.2.2']cryptand$^+$	− 6.2

4. Lineshapes and Linewidths

In general, lineshapes are true lorentzian (Fig. 3). Super-lorentzian lines are observed only in special cases (see Section 5). A lorentzian absorption is characterized by its height (I_{rel}), and width at half-height $\Delta\nu_{1/2}$. In the fast modulation region, *viz.* when the longitudinal T_1 and transverse T_2 relaxation times are equal, the peak height is directly proportional to the Na^+ concentration in the sample[51] (Fig. 4).

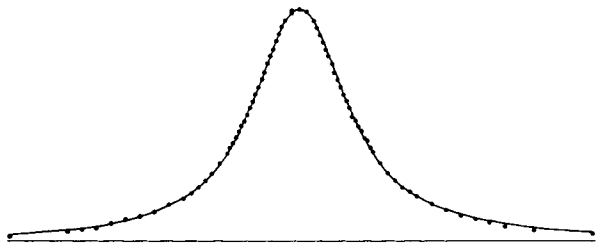


Fig. 3. Lineshape of a ^{23}Na-NMR signal. The curve is the actual experimental absorption; the points are calculated for the best lorentzian curve with identical width at half-height.

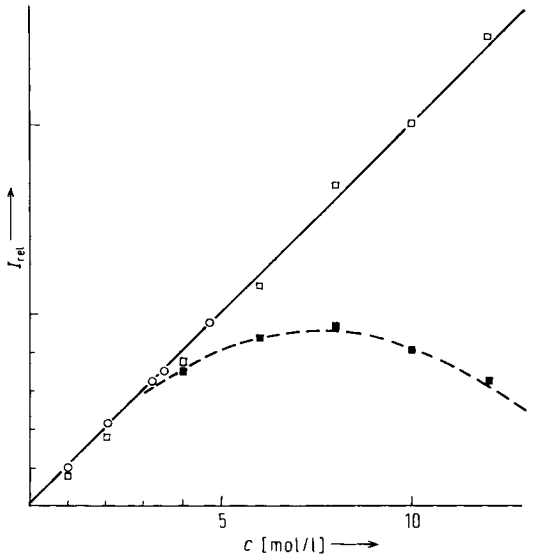


Fig. 4. Peak height (I_{rel}) of the ^{23}Na-NMR signals in aqueous solution. ○ NaCl; ■□ NaOH; (□ optimized γH_1 amplitude, ■ γH_1 constant). The peak height is an arbitrary unit, chosen to make the slope equal to one [51].

The linewidth $\Delta\nu_{1/2}$ is related to T_2, by:

$$\Delta\nu_{1/2} = \frac{1}{\pi T_2} \qquad \text{(a)}$$

If T_1 is indeed equal to T_2 because of motional narrowing, a linewidth measurement ($\Delta\nu_{1/2}$) is more practical and is equally as accurate as the direct determination of a relaxation time[52] (Fig. 5).

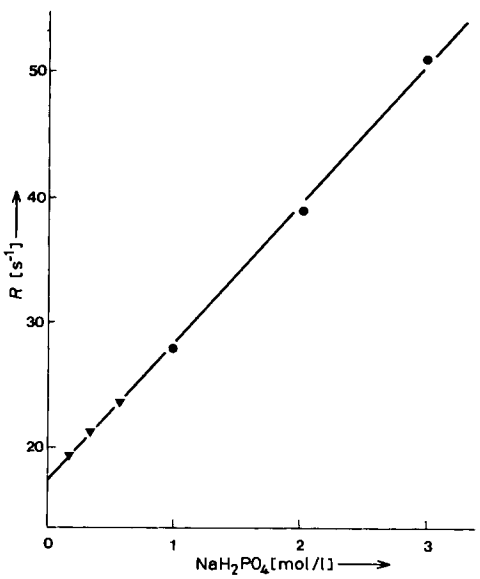


Fig. 5. Comparison of relaxation rates R, determined either from the linewidth (▼) or from a T_1 measurement (●). Sample: aqueous NaH_2PO_4 solution [52].

For instance, measurement of the linewidth of the ^{23}Na-signal in a sample of sodium heparinate at 62.86 MHz gives a value of 60 Hz, corresponding to a T_2 value of 5.305 ms. The longitudinal relaxation time T_1 is measured separately: $T_1 = 5.08$ ms. Given uncertainties of 5 % on the linewidth determination and of 10 % on the evaluation of the relaxation time, the agreement is indeed satisfactory[53].

In many cases, linewidths vary linearly with the bulk viscosity of the sample. For example, if NaCl is dissolved in a water/glycerol mixture (whose viscosity can be altered by a factor of 20 by altering the composition), the linewidth of the ^{23}Na-signal closely follows the viscosity, within ±30 %[54] (Fig. 6).

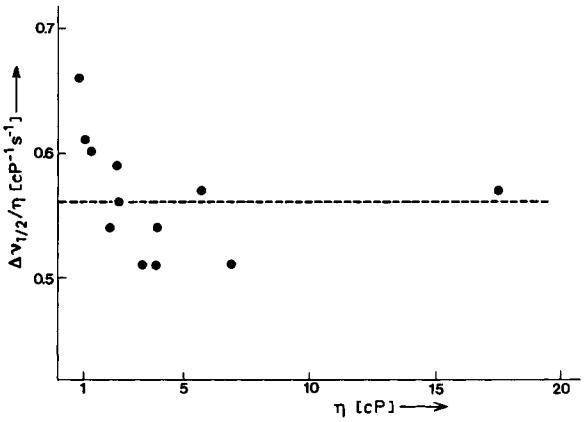


Fig. 6. A plot of the linewidth divided by the viscosity as a function of viscosity for water/glycerol mixtures; the dashed horizontal line corresponds to ideal Debye-Stokes-Einstein behavior. Sample: NaCl.

Hence, a standard procedure is to correct the relaxation rates $R_i = T_i^{-1}$ $(i = 1,2)$ for changes in relative viscosity[55], by normalizing the observed linewidths (or relaxation times) to a standard viscosity.

5. Mechanism of Quadrupolar Relaxation[56]

Since its spin number is greater than unity ($I = 3/2$), sodium-23 has an electric quadrupole moment eQ: the nucleus distorts, and instead of a spherical distribution of charge, we have a prolate or oblate ellipsoidal distribution of charges.

In the presence of an electric field gradient eq at the nucleus, *i. e.* whenever the distribution of electric charges in the sodium coordination sphere is asymmetric, an interaction is set up; the product $\chi = (eQ \cdot eq)/\hbar$ has the dimension of an energy, is called the quadrupole coupling constant, and in the case of the sodium-23 nucleus is of the order of 1 MHz.

With a spin number $I = 3/2$, the ^{23}Na nucleus can assume $2I + 1 =$ four orientations in a magnetic field $\mathbf{B}_0$. The projections of the spin vector I along the $\mathbf{B}_0$ axis have the values $m_I = -3/2, -1/2, +1/2$ and $+3/2$. The transitions between the corresponding energy states are degenerate in the absence

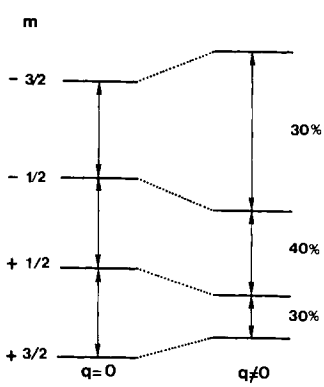


Fig. 7. Energy states for a spin 3/2 nucleus in the absence (left) and in the presence (right) of a quadrupolar interaction.

of an electric field gradient at the nucleus ($q=0$). The degeneracy is lifted by the quadrupolar interaction ($q\neq 0$) (Fig. 7).

The resultant three transitions should show up as three equidistant lines, the central line with 40% of the total intensity, and the outer lines having each 30% of the total intensity. The distance between two consecutive lines is

$$\frac{e^2qQ}{\hbar}\cdot\frac{(3\cos^2\theta-1)}{4}$$

where θ is the angle between the magnetic field $\mathbf{B}_0$ and the direction of the electric field gradient q.

In normal liquids, this angle θ fluctuates over all possible values due to fast reorientational motions. For isotropic rotational diffusion, with a vanishing asymmetry parameter for the electric field gradient, and with extreme motional narrowing, the three transitions collapse to a single line having a linewidth $\Delta\nu_{1/2}$. The relaxation rate $R_i=T_i^{-1}$ $(i=1,2)$ is then given by:

$$R_i=\pi\Delta\nu_{1/2}=\frac{2\pi^2}{5}\left(\frac{e^2qQ}{\hbar}\right)^2\cdot\tau_c \qquad \text{(b)}$$

where τ_c is a correlation time describing the reorientation of the quadrupolar interaction between the ^{23}Na nucleus and the local electric field gradient.

Equation (b) can be employed in many applications, and is the only one we shall discuss in this introductory and general presentation. It relates the experimentally accessible quantity $\Delta\nu_{1/2}$ to the product of two distinct unknowns: the quadrupole coupling constant χ and the correlation time τ_c.

In many liquids[57,58], and in aqueous solutions[59,60], at atmospheric pressure, reorientational correlation times for solute or solvent molecules increase linearly with the ratio of the shear viscosity to temperature η/T. Quantitative, or semi-quantitative, agreement with the Debye-Stokes-Einstein model[61]:

$$\tau_c=f_r\frac{V\eta}{k_BT};\ f_r=1$$

is obtained, provided the microviscosity factor f_r[62] is given a value of *ca.* $\frac{1}{5}$[50], between the values characteristic of the slipping[63] or sticking[64] solute-solvent boundary conditions.

Likewise there exist systems in which the sodium-23 relaxation R_i is affected predominantly by viscosity changes in the solution and the corresponding variations in the correlation time τ_c, while alterations in the quadrupole coupling constant χ can be neglected[25,54,65-66]. However, in order to derive values either for the correlation time τ_c or for the interaction energy χ from the measured linewidth $\Delta\nu_{1/2}$, a precise knowledge of the other term—either χ or τ_c—is necessary.

Take the problem of evaluating the quadrupole coupling constant χ, which is "a measure of the electric-field gradient at the nucleus, a quantity usually negligible to first order in other experiments. Thus, one has a rather unique probe with which to determine the charge distribution around the solute species (Na^+) of interest. Unfortunately, it is very difficult to compute the field gradient at the nucleus in terms of the charge distribution outside the ion because of the large and intractable effect of the closed-shell electrons, the so-called antishielding factor"[67].

It does not suffice to calculate the electric field gradient q at the sodium nucleus: the 1s, 2s and 2p electrons are polarized by the electric field from the adjoining point charges. This distortion of the electronic distribution around the sodium nucleus effectively magnifies the active field gradient by a factor $1-\gamma_\infty$, the antishielding Sternheimer factor[68-70], which has a value of 5.1—5.8 for ^{23}Na[71,72] (see also the Appendix).

It is then straightforward to compute for a electrostatic model[68,73,74] the quadrupole coupling constant arising from a point charge Z (a.u.) at a distance r(m) from the quadrupole moment Q(m^2) through an intervening dielectric (ε):

$$\chi=\frac{0.52\times10^6}{3I(2I-1)}\cdot(1-\gamma_\infty)\cdot\frac{2\varepsilon+3}{5\varepsilon}\cdot\frac{QZ}{r^3} \qquad \text{(c)}$$

Equation (c) can be applied to the interaction of hydrated Na^+ with an anionic end-group such as $-CO_2^-$ or $-SO_3^-$: at a distance of 4.9 Å, corresponding to the solvent-separated ion pair, the quadrupole coupling constant χ has a value of 0.011 MHz, according to this approach[75]. Similar treatments are applicable when the sodium ion interacts with a dipole, rather than with a point charge[68,73-75].

If however the sodium cation is surrounded by four or six identical solvent molecules, then there cannot be any contribution to a local electric field gradient from this first solvation sphere with tetrahedral or octahedral symmetry. One would then expect, from equation (b), a vanishing sodium-23 linewidth in pure solvents in which Na^+ is symmetrically solvated[67]. This expectation is not fulfilled, and finite linewidths obtain[76-83]. Why? What is the origin of the electric field gradient, when the first-order terms cancel, and only second-order terms are present?

Various models have been proposed. In the collision model, an electric field gradient occurs at each ion-solvent molecule collision, with attendant loss of spherical symmetry of the ion[39,41]. In the solvent exchange model, migration of a solvent molecule from the first solvation sphere into the bulk solution creates a vacancy: the electrostatic field gradient arises from coordinative unsaturation[84]. Thirdly, in the electrostatic model, the electric field gradient at the nuclear site is caused by the electric point dipoles of the surrounding solvent molecules and the point charges of other ions present in solution[78,85,86]. The electronic distortion is incorporated in this model, not as a specific effect, but through the Sternheimer multiplication factor[68-70]. The electrostatic model accounts successfully for a wide variety of experimental results relative to relaxation rates of quadrupolar nuclei[72,87-92].

Hubbard has pointed out that relaxation of spin $\frac{3}{2}$ nuclei should occur, not as a simple exponential decay, but rather as the sum of two exponentials[93,94]. In practice, deviation from a single exponential is often very small[92]. However in systems such as biological tissues, in which anisotropic regions may extend through distances of the order of 100 Å, and the motional narrowing condition is not obeyed, the residual triplet splitting (Fig. 7) shows up in the sodium-23 resonance signal as a super-lorentzian absorption, with prominent wings. Deconvolution of such a line yields a sharp

component, with 40% of the total intensity, superimposed upon a broader line which accounts for 60% of the total intensity (Fig. 7). These two lines correspond in width to the two distinct exponential curves, with differing relaxation times[93]. A number of investigators concluded from such observations, too hastily, the presence of *ca.* 40% Na^+ ions in the free state, and 60% in a bound state, attached to biological macromolecules[95–107]. In actual fact[108,109], cellular Na^+ ions are surprisingly unrestrained, despite the microviscosity of their environment, and their motion is slowed down by a mere factor of 3 to 8 compared to extracellular ions: Na^+ ions are essentially free in biological tissues[110].

Back to the problem of evaluating the quadrupole coupling constant χ [Eq. (c)]! There are two agencies enabling a good estimate of the viscosity-dependent correlation time τ_c to be made. One is with ionophores, in which the correlation time for reorientation of the whole complex can be obtained from a separate probe such as T_1 values for ^{13}C or D nuclei: this approach has been applied to cryptates[29], yielding a linear correlation between the ^{23}Na chemical shift and the quadrupole coupling constant χ[50]. The second involves tight ion pairs in which both partners rotate as a unit[111]; again it is possible to determine the correlation time in the anion from ^{13}C or D relaxation times. This procedure has been applied by us to the sodium salt of 5′-adenosine monophosphate[112]: comparison of the ^{23}Na linewidth of 50 Hz with the correlation time of 140 ps, derived from the ^{13}C T_1 values[113], yields a χ value of 0.5 ± 0.1 MHz for Na^+ complexed to a monophosphate in water solution.

6. Application to Characteristics of Na^+ Solvation

Interactions between the sodium cation and its ligands are almost purely electrostatic[44–46,114], and lack directional character. Given the opportunity, Na^+ wraps itself into a sheath of coordinating molecules and draws their donor atoms, such as oxygen or nitrogen, to within van der Waals contact. Sodium-oxygen distances of 2.4—2.6 Å, closely corresponding to the sum of the ionic radius of Na^+ (0.95 Å)[115] and the van der Waals radius for oxygen (1.40 Å), are frequently observed on X-ray structural analysis of Na^+ complexes with crown ethers and ionophoric antibiotics[116–121]. Water molecules occupy the remaining vacant sites at Na—O distances between 2.29 and 2.35 Å[122], very close to the values calculated by *ab initio* methods[45].

Hydration numbers for the Na^+ cation in the range 3—6 have been obtained from a variety of methods, including sodium-23 chemical shifts and relaxation measurements, and with different assumptions[25,45,46,89,123–129]; whereas the hexaaqua ion exists in the gas phase[45,46,128], a coordination number closer to 4 is more likely in aqueous solutions[25,89,125,126]. This coordination number of 4 applies also for solvation with somewhat more voluminous solvent molecules such as methanol[126], tetrahydrofuran[130–131], dimethyl sulfoxide[132], dimethyl acetamide[132], and pyridine[133]. For the more bulky hexamethylphosphoric triamide, a solvation number of 3 has been reported[134,135].

Measurement of the ^{23}Na linewidth for $NaClO_4$ in a series of oxygen-containing ether and alcohol solvents displays Debye-Stokes-Einstein behavior, and yields a Stokes radius for the solvated Na^+ of 3.6 ± 0.7 (3σ) Å[65], in accord with the conductimetric measurements by *Szwarc et al.*[136] of 3.95 ± 0.5 Å (THF) and 3.2 ± 0.4 Å (monoglyme = 1,2-dimethoxyethane); the Monte Carlo value for $Na^+(H_2O)_6$ is 3.4 ± 0.3 Å[129]. The corresponding NMR Stokes volume of $120 \pm 20\,ml \cdot mol^{-1}$ is clearly much too small for the rigid assembly[137] of four THF molecules or two monoglyme molecules (each with two oxygens) coordinated to the sodium cation. One is dealing instead with a spherical particle centered on sodium, of radius *ca.* 3.75 Å. This value can be regarded as the sodium-oxygen distance (*ca.* 2.35 Å) augmented by the van der Waals radius of the oxygen atom (1.40 Å): the sodium solvation shell is kinetically labile; fast exchange of solvent molecules between the first solvation sphere and the bulk of the solution proceeds at a rate commensurate with that of the overall reorientational motion[84], while maintaining the oxygen heteroatoms at van der Waals contact with the Na^+ ion. In the solvation shell, water or methanol solvent molecules indeed turn their dipoles towards the sodium cation[72].

Competition between different donor solvent molecules for coordination to the sodium cation is easily studied using ^{23}Na-NMR spectroscopy. The change in the ^{23}Na chemical shift can be monitored as a function of composition in binary

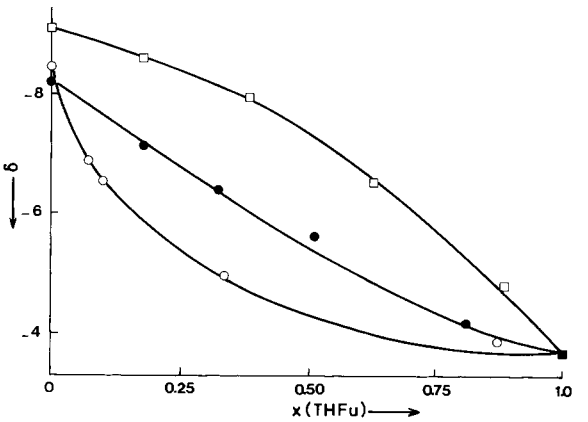


Fig. 8. ^{23}Na chemical shift for $Na^+ClO_4^-$ in binary mixtures of monoglyme (○), diglyme (●) and triglyme (□) in competition with 2-tetrahydrofuranmethanol (THFu), as a function of composition (given as mole fraction x (THFu)) [137]. In a qualitative sense, diglyme is almost as good a donor as 2-tetrahydrofuranmethanol, monoglyme is worse, and triglyme is better.

solvent mixtures (Fig. 8)[138]. Preferential solvation by one of the component solvent molecules occurs[32,139,140]. The iso-solvation point[141] is the midpoint between the chemical shifts in the pure A and B solvents. It serves as an index for preferential solvation: for instance, the sequence

$$[(CH_3)_2N]_3PO \gg [(CH_3)_2N]_2CO > (CH_3)_2SO > C_5H_5N > CH_3CN \gg CH_3NO_2$$

has been obtained[140]. It represents the solvating ability of a solvent in a mixture. Pure solvents can be highly structured, to the detriment of their apparent donor ability: dimethyl sulfoxide is a prime example[142].

A more quantitative treatment, first proposed by *Stengle et al.*[141] and fully developed by *Covington*[143] assumes stepwise displacement of solvent A by solvent B, and that the

observed chemical shift is the weighted average for the species present and changes by the same increment whenever a B molecule removes an A molecule from the coordination sphere. This treatment also demands that solvents A and B have similar dielectric constants, that the solutions be ideal, and that the equilibrium constants for the successive equilibria be related only statistically[132]. Whereas all the examples of sodium solvation that have been studied so far appear to satisfy these conditions[138–140], one case of Ag^+ solvation shows breakdown of the incremental chemical shift hypothesis[144].

In mixtures of tetrahydrofuran and 2-tetrahydrofuran methanol (THFu), a bidentate ligand, the ^{23}Na chemical shift changes monotonically with the composition. Of the following models: 4THF → 4THFu, 4THF → 3THFu, 4THF → 2THFu, only the latter accounts for the observed data. It is the only model consistent with tetracoordination of Na^+ by the oxygen heteroatoms in the solvent molecules[145]. Thermodynamic parameters are derived from the data, and the values of $\Delta G°$ for transfer of Na^+ between the various solvents[138, 145]:

$$THF < CH_3OH < monoglyme < diglyme < triglyme < glycol$$

follow a sequence very close to that observed by *Arnett et al.*[146] for the calorimetric heat of complexation of Na^+ by hydroxy and ether solvents, in acetone solution:

$$THF < methanol < monoglyme < diglyme < glycol < triglyme$$

The sodium-23 chemical shift itself (for sodium tetraphenylboron) gives an excellent correlation with the free energy of transfer (of sodium chloride) from pure water in a series of binary water/glycerine diacetate mixtures[147].

In Covington-type treatments[143] symmetry numbers for the various pathways interconverting the limiting structures $(Na^+)_{mA}$ and $(Na^+)_{nB}$ present in the pure A and B solvents are extracted from the experimental data. Their comparison with calculated values leads to inferences about the nature and number of intermediate structures: for instance, in the competition between THFu and the glymes, a single bicyclic intermediate is present with diglyme and triglyme, while several monocyclic intermediates occur with monoglyme—presumably because of angular constraints[138]. Examination of the ^{23}Na-NMR linewidths, corrected for viscosity changes, confirms this conclusion[148].

In comparison to the symmetrical limiting structures $(Na^+)_{mA}$ or $(Na^+)_{nB}$, intermediate structures with solvation shells made up partly of A molecules, partly of B molecules, lack symmetry. In the less symmetrical structures the resulting electric field gradient translates (Section 5) into significant increases of the linewidth[149], which in turn can be used as an independent confirmation of conclusions based upon chemical shifts. Often, in ^{23}Na-NMR spectroscopy, chemical shifts and linewidths mutually check one another, thus making it a highly reliable tool. It then becomes possible to ascertain the mechanism of $A \rightleftharpoons B$ solvent exchange: an associative mechanism is consistent with the data obtained in binary mixtures of THFu with THF, the glymes and other oxygenated solvents[138, 148].

7. Application to the Structure and Microdynamics of Ion Pairs

A fundamental dichotomy is that between *tight* and *loose* ion pairs, with a number of operational criteria to distinguish between either structural type on the basis of spectroscopic data or reactivity measurements[150].

^{23}Na-NMR spectroscopy can also be applied, often with interesting results. For instance, the ^{23}Na absorptions for $NaB(C_6H_5)_4$ appear consistently 6—8 ppm upfield from those of $NaBH_4$ (both in ether solutions[66]). Also, the tetraphenyl borate (but not the hydroborate) has a concentration-independent chemical shift in numerous non-aqueous solvents[33–36]. These convergent criteria point to the existence of a loose ion pair $Na^+[B(C_6H_5)_4^-]$ in solvents such as the glymes[151]; this conclusion agrees with previously obtained evidence from conductimetry and optical spectroscopy[25,150].

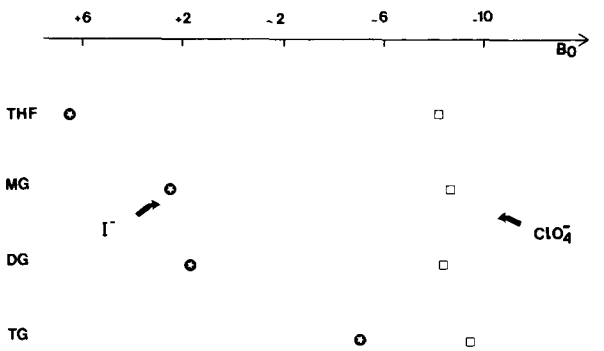


Fig. 9. Solvent-dependence of the ^{23}Na chemical shift of Na^+I^- and $Na^+ClO_4^-$: in tetrahydrofuran (THF), monoglyme (MG), diglyme (DG), and triglyme (TG) [152].

Also interesting is the comparison between $NaClO_4$ and NaI (Fig. 9): the perchlorate exists as loose, solvent-separated ion pairs in THF and the glymes. For the iodide, tight ion pairs predominate in THF, and loose ion pairs in triglyme, with intermediate positions of the tight⇌loose equilibrium in monoglyme and diglyme[152].

Replacement in the sodium coordination sphere of the counter-ion by a solvent molecule leads to a high-field shift when the anion is a better electron donor than the solvent molecules[153]. A down-field shift is observed when the anion is a poorer electron donor than solvent molecules[153]. Such is the case with highly delocalized anions (ClO_4^-, PF_6^-, $B(C_6H_5)_4^-$) when displaced by solvent molecules which are better donors[153].

The observation of tight or loose ion pairs depends markedly upon the nature of the solvent: for NaI, the concentration-independence of the chemical shift led *Popov*[36] to conclude the presence of loose ion pairs in DMSO, while in the iso-dielectric solvent sulfolane tight ion pairs are present, as follows from the concentration-dependent chemical shift. The relevant characteristic is the donor ability: the donor numbers are 29.8 for DMSO *versus* 14.8 for sulfolane.

Aggregation of tight ion pairs introduces a second counter ion in the sodium coordination sphere, and therefore affects the chemical shift. For instance, sodium iodide shows a concentration-dependent chemical shift in THF solution (Fig. 10),

which we analyzed[152] in terms of predominant dimer formation. These $(NaI)_2$ species are characterized by a Stokes radius of *ca.* 5 Å, significantly higher than that of 3.7 Å for the Na^+ cation (from $NaClO_4$) solvated also by THF molecules[65].

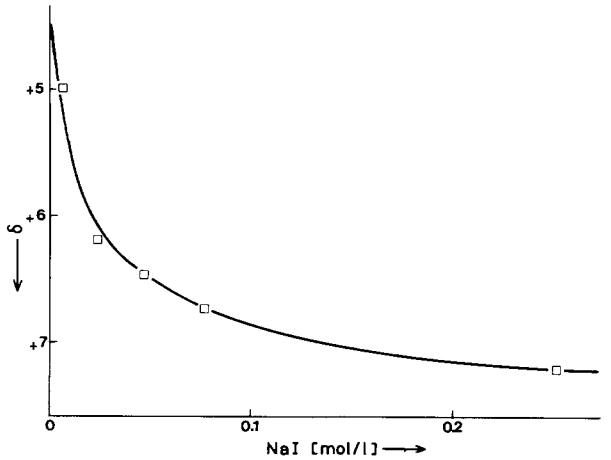
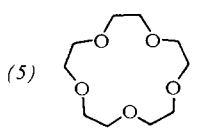
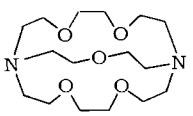


Fig. 10. Change in ^{23}Na chemical shift as a function of concentration (for NaI in THF): the resonance moves upfield with decreasing concentration [152].

When a tight A^-, Na^+ ion pair is co-dissolved with a sodium-specific neutral ligand, such as the crown ether



(5)



(2)

[15]crown-5 *(5)*[154] or the [2.2.1]cryptand *(2)*[29], the following equilibria are present (L = ligand molecule)[155,156]:

$$A^-, Na^+ + L \rightleftharpoons A^-, Na^+, L$$
$$A^-, Na^+ + L \rightleftharpoons A^-, L, Na^+$$
$$A^-, Na^+, L \rightleftharpoons A^-, L, Na^+$$

The externally-perturbed ion pair A^-, Na^+, L coexists with the internally-perturbed (separated) ion pair A^-, L, Na^+. Thus, *e.g.*, the reactivity of the sodium enolate of ethyl acetoacetate on alkylation with reagents such as C_2H_5I is greatly increased in the presence of one equivalent of the [2.2.2]cryptand *(3)* or 10 equivalents of [18]crown-6 ether, and becomes equivalent to that of the free ion[157,158]. Intuitively, the species

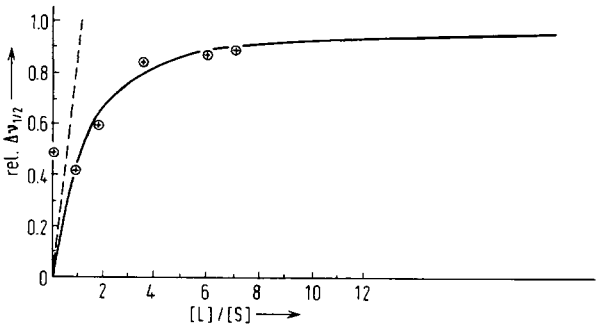


Fig. 11. Normalized linewidth rel. $\Delta\nu_{1/2}$ of the ^{23}Na-NMR signal of the sodium enolate of ethyl acetoacetate (S) as a function of added [2.2.1]cryptand *(2)* (L) in THF solution containing 10 % C_6D_6 at 30 °C. This plot corresponds to limiting values of the normalized linewidth of 1917 $cP^{-1}s^{-1}$ in the absence of L and of 136 $cP^{-1}s^{-1}$ for sodium cryptate. The equilibrium constant for sodium cryptation in this experiment is 161/mol.

to be associated with the highest reactivity ought to be the internally-perturbed A^-, L, Na^+ ion pair. Indeed, chemical shifts and normalized linewidths (Fig. 11) strongly suggest[159] that the dominant species in the presence of more than one equivalent of the cryptand is the cryptand-separated ion pair in which the sodium cation is cryptated, thus increasing the reactivity of the counter-ion. When L is the [15]crown-5 ether, a crowned ion pair A^-, Na^+, L appears to be formed[159], with a reactivity equivalent to that of the free anion[160,161].

In aqueous solutions, sodium salts dissociate almost completely. In general, the ^{23}Na chemical shift differs little from that for the free sodium ion under the same conditions. Fortunately, the ^{23}Na linewidth is highly sensitive to the restriction of reorientational motion caused by ion pairing; even small amounts of ion pairs can thus be detected quite reliably. This is illustrated for phosphate counter-ions by the pH dependence of the ^{23}Na relaxation rate (Fig. 12)[162].

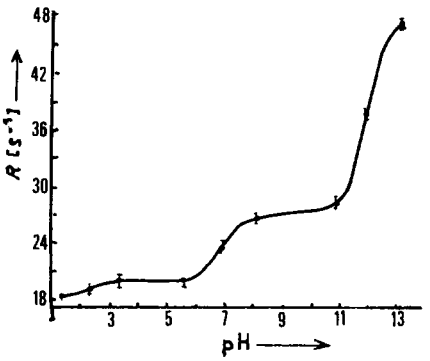
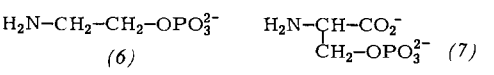


Fig. 12. pH-dependence of ^{23}Na relaxation rate $R_1 = 1/T_1$ in NaCl/sodium phosphate solutions (0.20 mol/l) [162].

The sodium cation binds to PO_4^{3-} above pH = 13, to HPO_4^{2-} between pH = 8 and 11, and to $H_2PO_4^-$ between pH = 3 and 6; the pK_a values for the successive ionizations of phosphoric acid are 2.1, 7.2 and 12.4[163], in good agreement with the inflexion points in the titration curve of Figure 12. This curve suggests a limiting value of *ca.* 50 Hz for binding to the PO_4^{3-} ion. Using the literature value $\log\beta = 0.59$ (at 25 °C)[164] for the global equilibrium

$$PO_4^{3-} + 3\,Na^+ \overset{\beta}{\rightleftharpoons} PO_4^{3-}, 3\,Na^+$$

and 5 Hz as the linewidth characteristic of *free* sodium, one obtains a relaxation rate R_1 for *bound* sodium of *ca.* $80\,s^{-1}$ which, together with the quadrupole coupling constant $\chi = 0.5$ MHz appropriate for interaction of Na^+ with a phosphate group[112], leads to a correlation time τ_c of about 70 ps for reorientation of the PO_4^{3-}, Na^+ pair. By comparison, the correlation time for reorientation of $PO_3F_2^-$—a somewhat similar system—is *ca.* 40 ps[165], *i.e.* of the same order of magnitude.



(6) *(7)*

James and *Noggle*[162] have used 2-aminoethyl phosphate (phosphoethanolamine) *(6)* and *O*-phosphonoserine *(7)* as

models for the basic moieties of two prominent phospholipidic carriers in membranes: binding of Na^+ follows the sequence phosphate > *O*-phosphonoserine > phosphoethanolamine, and correlates directly with the charge-to-radius ratio of the anions. However, Na^+ interacts only weakly with the potential carrier phosphatidyl serine, in the form of an aqueous dispersion, at physiological pH[162].

There are many experimental situations in which the sodium cation is in rapid exchange between *free* and *bound* states. The observables, either a chemical shift or a linewidth, are the weighted average quantities. For instance, the relaxation rates $R_i = 1/T_i$ $(i = 1,2)$ are related, as in the cases above, by:

$$R_{(i)\,obs} = x_f R_{(i)\,f} + x_b R_{(i)\,b}$$

where subscripts f and b refer to the *free* and *bound* states respectively, and the x are mole fractions.

Binding of the sodium cation to biological molecules has special importance, and is dealt with in the following section.

8. Application to the Binding of Na^+ and Other Cations to Biomolecules

Historically, *Jardetzky* and *Wertz*[77] were the first to investigate complexation of Na^+ by organic chelating ligands. The observed line broadenings[77] correlate with stability constants K_f for the complexes, as obtained by potentiometric titration using ion-sensitive glass electrodes[166]: the values of K_f range from 0.2—0.3 for amino acids such as DL-alanine or L-leucine through 1.9 for malic acid to 2.7 for pyruvic acid.

These early findings[77] on a very extensive series of samples, including the contents of a hemolyzed red blood cell, were indeed sufficiently exciting that other groups entered the field. *Eisenstadt* and *Friedman*[167] examined further the ion pairing of Na^+ with sulfate. *James* and *Noggle*[168] conclude, contrary to *Jardetzky* and *Wertz*[77], that the Na^+-histidine interaction is very weak. Assuredly, the *Jardetzky* and *Wertz*[77] exploratory linewidth measurements were made in the face of substantial magnetic field inhomogeneity[167], which does not appear to explain the failure of *James* and *Noggle*[168] to find a histidine complex.

From the pH dependence of the relaxation rate R_1, stability constants K_f are obtained[168] (25 °C; $\mu = 0.7$—1.0) for *N'*-(2-hydroxyethyl)ethylenediamine-*N*,*N*,*N'*-triacetic acid (HEEDTA, $K_f = 8.7 \pm 0.9$ l/mol) and for nitrilotriacetic acid (NTA, $K_f = 9.6 \pm 1.5$ l/mol). Using the calculated R_1 values for the *bound* state, the quadrupole coupling constant χ for the Na^+-aminopolycarboxylate complexes in aqueous solution is about 4 MHz[168].

Na^+-binding to simple carbohydrates in aqueous solution is very weak, unless an axial-equatorial-axial sequence of OH groups is present[169–171]; thus *Andrasko* and *Forsén* found significant ^{23}Na line broadenings only with *cis*-inositol ($K_f \simeq 1.2$ l/mol)[172]. In non-aqueous solvents with low dielectric constants, the interaction is both stronger and less specific. We have used amine solvents, such as pyridine or isopropylamine, in order to generate substantial electric field gradients at the sodium nucleus: Na^+ is coordinated on one face by nitrogen heteroatoms from solvent molecules, and on the other face by oxygen heteroatoms from two (or three) OH groups of the sugar molecule[173]. The stability constants K_f for the complexes are in the range 5—20 l/mol for a variety of simple carbohydrates[173]. In pyridine solution, at 290 K, the sodium linewidth characteristic of the complex increases from 800 ± 150 Hz for hexopyranoses to 2000 ± 400 Hz for the disaccharide lactose, in line with the expected approximate doubling of the reorientational correlation time as the molecular weight (volume) increases by a factor of about 2[174].

The interaction of Na^+ with polysaccharides has also been investigated. With heparin, a glycosaminoglycan, the pH dependence of the ^{23}Na linewidth, with an equivalence point of 4.5, indicates predominant binding by the carboxyl groups[53]. At least two carboxyl groups situated on different rings chelate a given Na^+ ion: the dissociation constants K_d for the ion pairs are in the range 5—20 mmol/l, *i.e.* weaker by an order of magnitude than the sodium binding by citrate ($K_d = 300$ mmol/l), using the same ^{23}Na-NMR technique[53]. Other cations bind to the same sites in competition with Na^+. For instance, in aqueous solution, Ca^{2+} forms much stronger complexes than Na^+ with a simple sugar such as ribose[172] or with a mucopolysaccharide such as heparin[53] (Fig. 13).

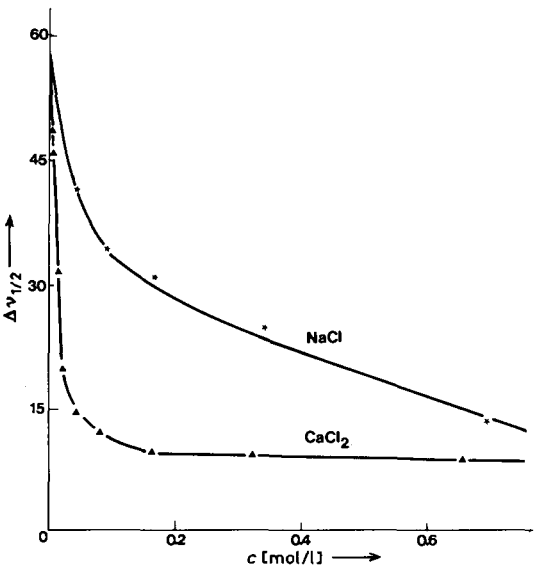


Fig. 13. Linewidth of the ^{23}Na-NMR signal of sodium heparinate as a function of added NaCl or $CaCl_2$ [53]. c = concentration of the respective salt.

From such competition experiments, taking advantage of the high sensitivity of ^{23}Na-NMR spectroscopy, one can study the binding of many inorganic and organic cations to biomolecules, by following the changes of the ^{23}Na linewidth as another cation is added to the solution. With heparin, for example, cation fixation follows the sequence: $Ca^{2+} > Cu^{2+} > Co^{2+} > Sr^{2+} > Mg^{2+} > Ni^{2+} > Be^{2+} > K^+ > NH_4^+ > Na^+ > Li^+ > N(CH_3)_4^+ >$ acetylcholine[53].

This finding that glycosaminoglycans bind cations at specific sites[53,175] is relevant to the long-standing question of site binding *versus* atmospheric binding in counter-ion binding to polyelectrolytes[176–178]. An illuminating analogy presents itself: tight ion pairs for site binding, and loose, solvent-separated ion pairs for atmospheric binding[179].

Leyte et al.[180–182,187,188] have conducted a joint experimental and theoretical study of the binding of alkali metal

ions by polyelectrolytes. The ^{23}Na relaxation rate for polyphosphates increases with the molecular weight of the polymer up to a degree of polymerization of about 60; it then remains constant[180,181]. This sets a lower limit to the applicability of the rigid rod model for a polyelectrolyte: the polymer is treated as a uniformly charged rod of radius a, from which originates a radially directed electric field. The relaxation rate is proportional to the average value of the square of this radial electric field acting on the sodium nucleus. Using the analytical solution of the Poisson-Boltzmann equation, an equation is derived for the relaxation rate of ^{23}Na in polyelectrolyte solutions as a function of the degree of neutralization α[182]. This leads to values of $a=2.8$ Å, too small to be physically realistic, since a should correspond to the sum of the hydrated radii of polyion and sodium counterion, *i.e.* 5.6 Å[183]. Hence the counterion condensation concept of *Manning*[184–186] is to be preferred: the net charge density of the polyion is maintained at a constant value by condensation (*i.e.* atmospheric binding) of the counter-ions; counter-ions will condense until this critical value is reached. Given a mean distance d between charged groups, the linear charge density parameter

$$\xi = \frac{e^2}{\varepsilon \cdot KT \cdot d}$$

is approximately equal to $7.1\,d^{-1}$ in water solution, with unit charges. The critical value is $\xi=1$; with $\lambda=\alpha\cdot\xi$ a fraction $(\lambda-1)/\lambda$ of the counter-ions condenses on the polyelectrolyte. This treatment predicts that the relaxation rate should increase proportionately to the square of the degree of neutralization α, as indeed observed for the Na^+-polyphosphoric acid interaction[187]. All the Na^+ ions are atmospherically bound on a polyphosphate rod, with a distance $d=2.6$ Å between charged groups, at a distance of *ca.* 3 Å from the axis[187].

Competition with divalent ions was also studied, using a polyelectrolyte characterized by $\lambda=2.85$. Ba^{2+} ions condense or bind on the poly-anion until the effective value of λ is $\frac{1}{2}$; excess Ba^{2+} and all Na^+ cations remain free in solution. Using ^{23}Na relaxation as an indirect means of monitoring Ba^{2+} interaction with poly(styrenesulfonic acid), the divalent ions condense with, rather than bind to the charged polymer[188].

Condensation of Na^+ ion around the charged polymer, rather than specific binding on well defined sites, also occurs with the nucleic acids: both with soluble RNA[189] as with DNA[190], the ^{23}Na relaxation rate increases from a value of *ca.* 18 Hz for free Na^+ to a value of about 170—220 Hz for bound Na^+. If the Na^+ ions were rigidly bound to the slowly reorienting nucleic acid macromolecule, the expected relaxation rate would be increased to a minimum of 15000 Hz. Furthermore, the correlation time inferred for the DNA-Na^+ system from measurements at three different frequencies is 5.5 ps[190], *i.e.* only marginally greater than for the hexaaqua ion. This led *Reuben*[191] to conclude: "Thus, because of short lifetimes of the macromolecular complexes of sodium, the relaxation rate of ^{23}Na cannot be used in studies of macromolecular dynamics in solution".

Obviously, such a sweeping statement should not and does not apply to macromolecular binding sites were two or more groups chelate the Na^+ cation. For instance, parvalbumin is a calcium-binding protein having two Ca^{2+} ions tightly bound ($K_d \approx 10^{-7}$ mol/l) per molecule (rel. molecular mass $\approx$ 12000). Removal of a single calcium ion maintains the conformational integrity of parvalbumin: the sodium cation attaches itself to the vacant binding site, with a binding constant $K=30$ l/mol; its apparent correlation time $\tau_c \approx 3\times10^{-9}$ s, very close to that of the protein as inferred from ^{13}C relaxation times[192], indicates that the cation-protein complex reorients as a single entity devoid of kinetic lability[193]: the lifetime of this complex is approximately 20 times longer than τ_c[193]. The *off* rate $k_- = 2\times10^7\,s^{-1}$ and the *on* rate $k_+ = 0.6\times10^9\,l\,mol^{-1}\,s^{-1}$.

The activation energies for decomplexation of Na^+ attached to macrocyclic polyethers in various solvents[194,195] and for cryptates in water[196] or ethylenediamine solution[28,197] are observed in a rather narrow range of 12.2 ± 1.1 kcal/mol.

From the ion pairing of Na^+ with phosphate groups, the self-assembly of the 5′-GMP nucleotide has been studied[112,198]: the apparent correlation time increases, depending upon the conditions, by a factor 20—50, corresponding closely to the degree of aggregation. Transition from the monomeric state to an ordered n-mer can be effected by decreasing the temperature[112], increasing the 5′-GMP concentration[112], or by the presence of K^+ ions[198]. These aggregates may have served as templates for the prebiotic appearance of nuclei acids[199].

9. Micelles and Membranes

The early 1970's saw several reports on the triplet splitting of the ^{23}Na resonance in liquid crystals[75,200,201]

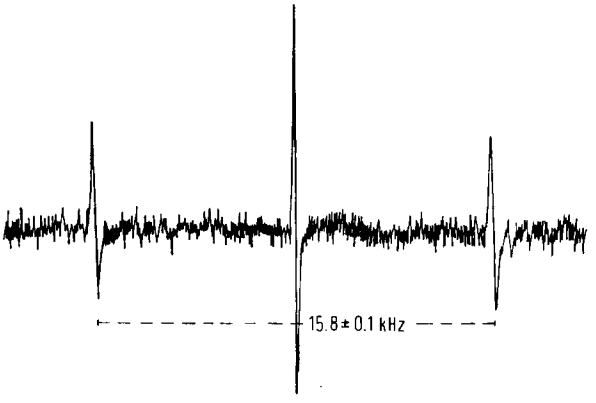


Fig. 14. ^{23}Na-NMR signal of a lyotropic nematic phase; frequency 8.0 MHz. The temperature of the probe was 26.4 ± 0.1 °C [201].

as a function of local order (Fig. 14). The Na^+ ions are attached, part of the time, to polar groups which are highly ordered. The quadrupole splitting reflects anisotropic motion over long times, *i.e.* greater than a microsecond. The separation between the outer lines is proportional to the product of the quadrupole coupling constant and an order parameter S[202], the degree of orientation of the electric field gradient axis.

It is thus possible to use counterion binding by Na^+ to explore the surface of mesophases and amphiphiles, and to derive information about local geometries. For instance, a separation of the counterion from the anionic polar heads by distances greater than 5 Å is characteristic for solvent-

separated ion pairs[75]. For surfactant mesophases containing a long-chain sodium alkyl sulfate or sulfonate, the order parameter S is close to unity[203]; this implies that the electric field gradient is colinear with the mesophase director, *i.e.* that the hydrated Na^+ interacts equally with the three oxygens, as expected from a simple RSO_3^-, Na^+ interionic attraction[75, 203]. Conversely, when the anionic amphiphiles have carboxylate end groups, the Na^+ ions insert themselves between the polar end groups; the electric field gradient and the director make an average angle close to the magic angle (54°44′), and S approaches zero[208, 209]. Numerous detailed studies have appeared[75, 204–210], exploiting these concepts on the basis of an excellent theoretical framework[203]. Mapping of the quadrupole interaction as a function of composition for ternary aqueous amphiphile solutions has been performed in a number of cases[209].

The critical micelle concentration (CMC) is readily apparent from the sharp change in the chemical shift (Fig. 15)[211] or in the relaxation rate[212]: when plotted against the inverse amphiphile concentration, it has the characteristic appearance of two straight line segments intersecting at the CMC. In order to account for such behavior, a two-site model is sufficient: there is fast exchange between the free and the bound Na^+. In addition, it is assumed that the pseudophase separation model describes micelle formation, and that condensation of the sodium counterions on the polar head groups is concentration-independent.

Multiple-quantum transitions have been encountered in the ^{23}Na-NMR spectra of lyotropic liquid crystals[213].

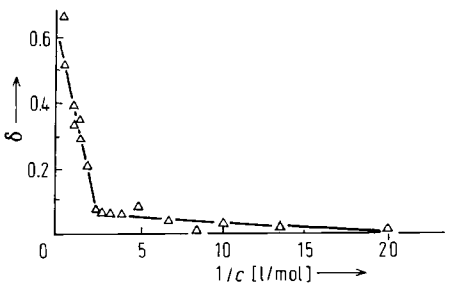


Fig. 15. ^{23}Na chemical shift as a function of the inverse concentration of a soap (sodium *n*-octanoate). Standard: 0.5 M NaCl [211].

10. And from There?

It is a useful exercise to look back at the 10 years or so during which applications of ^{23}Na-NMR spectroscopy have been explored. Sparse numbers of investigations characterize this period, at least until the advent of Fourier transform techniques. Often, slowly growing dissatisfaction follows an initial burst of enthusiasm. The reasons for this are numerous: the lack of understanding of the components of the chemical shift, the necessity of gathering a wealth of extraneous data such as magnetic susceptibilities, equilibrium constants, viscosities, *etc.* which complicates measurements and which precludes immediate answers, the under-development of model calculations for the quadrupole coupling constant. All contribute to this unhappy state of the art.

Further, chemists have been used to nuclear magnetic resonance of covalently-bound nuclei (^{1}H, ^{13}C, ^{19}F, ^{31}P ...), and are less familiar with the leaps and bounds of an ion fancying itself as a free agent.

However, this very conceptual break may prove itself the saving grace for ^{23}Na-NMR spectroscopy: the electrostatic interaction commends itself by its extreme simplicity. Thus the difficulties pointed out in the preceding paragraph might be overcome by relatively easy solutions, and I foresee an explosive growth in the field of ^{23}Na-NMR spectroscopy in the years to come. It may even be exploited in the building of scanners for malignant tumors[214]!

Appendix

Since a variety of numbers have been quoted in the literature for the ^{23}Na quadrupole moment Q (as well as for the Sternheimer anti-shielding factor $(1-\gamma_\infty)$), differing by up to 50 %—which will lead to a 100 % discrepancy in estimates of T_2 or the linewidth $\Delta\nu_{1/2}$—we have undertaken a critical survey. We feel that values of Q close to 0.15 barn (0.15×10^{-24} cm^2) are erroneous[215–219]. Taking the experimental values obtained for the atom in the 3p or 4p state[220, 221], and corrected for the anti-shielding contribution, yields values of $Q=0.10\times10^{-24}$ cm^2[222], in excellent accord with results from calculations[223]. The Sternheimer anti-shielding factor $(1-\gamma_\infty)$ has a value close to 5.8[222, 224], somewhat larger than previously-quoted figures[72, 75, 225].

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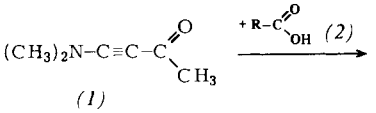
Communications are brief preliminary reports of research work in all areas of chemistry which, on account of its fundamental significance, novelty, or general applicability, should be of interest to a broad spectrum of chemists. Authors of communications are requested to state reasons of this kind justifying publication on submission of their manuscript. The same reasons should be clearly apparent from the manuscript. In cases where the editorial staff decide, after due consultation with independent referees, that these conditions are not met, manuscripts will be returned to the authors with the request to submit them for publication in a specialist journal catering for scientists working in the field concerned.

A New Method for Selective Activation of Amino, Hydroxy, and Mercapto Carboxylic Acids at the Carboxyl Group: Preparation of Thiol and Selenol Esters

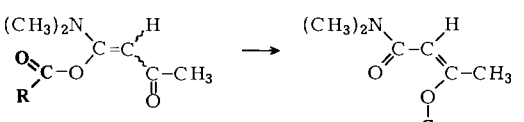
By *Hans-Joachim Gais* and *Thomas Lied*[*]

Synthetic objectives in the field of macrolides prompted us to search for new very mild methods of broad applicability for the chemoselective activation of polyhydroxy carboxylic acids—a key reaction in the lactonization of macrolide seco-acids. We now report such a procedure for activating amino, hydroxy, and mercapto carboxylic acids by transformation into activated enol esters *(4)* with 4-dimethylamino-3-butyn-2-one *(1)*[1] and their use as acyl transfer reagents in the synthesis of thiol and selenol esters *(5)* and *(6)*, respectively.

The acetylene derivative *(1)*, readily accessible by reaction of 4-dimethylamino-3-buten-2-one[2] with bromine and subsequent elimination of HBr, reacts with an equimolar amount of benzoic acid *(2a)* in tetrahydrofuran in the presence of a 100-fold excess of methanol, ethanol, 2-propanol, or *tert*-butyl alcohol at −60 to 0°C with exclusive addition of the carboxyl group to the triple bond. The primary adduct *(3a)* is not isolable; it rapidly rearranges quantitatively[1,3] to *N,N*-dimethyl-(*Z*)-3-benzoyloxycrotonamide *(4a)* which can be isolated in >95% yield. No addition of *(1)* to alcohols is observed[4].



(1)



(3) *(4)*

After prolonged reaction in the presence of an equivalent amount or an excess of benzylamine, *(1)* and *(2a)* do not give *(4a)* but, apart from *N,N*-dimethylacetoacetamide, *N*-benzylbenzoamide in 96% yield. Selective formation of *(4a)* is followed in this case by acyl transfer[5] with amide formation[6].

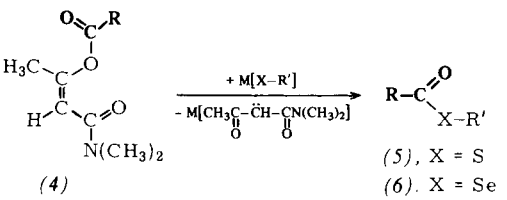
Reaction of structurally highly diverse hydroxy carboxylic acids *(2b—o)* [with primary, secondary, and tertiary alcoholic and phenolic OH groups] and amino *(2p—r)* and mercapto acids *(2s)* with *(1)* at −50°C in anhydrous tetrahydrofuran leads rapidly and almost quantitatively to the corresponding enol esters *(4)* (Table 1)[7].

Table 1. Synthesis of enol esters *(4)* from *(1)* and *(2)*.

	Carboxylic acid *(2)*	Enol ester *(4)*	Yield [%]
(b)	Mandelic acid	*(b)*	96
(c)	α-Hydroxycyclohexanecarboxylic acid	*(c)*	93
(d)	Glycolic acid	*(d)*	93
(e)	Quinic acid	*(e)*	94
(f)	D(−)-Tartaric acid	*(f)*	98 [a]
(g)	12-Hydroxystearic acid	*(g)*	95
(h)	Ricinelaidic acid	*(h)*	96
(i)	(*Z*)-L-Serine	*(i)*	97
(j)	Cholic acid	*(j)*	98
(k)	*p*-Hydroxyphenylacetic acid	*(k)*	96
(l)	*p*-Hydroxycinnamic acid	*(l)*	97
(m)	Salicylic acid	*(m)*	97
(n)	*m*-Hydroxybenzoic acid	*(n)*	93
(o)	*p*-Hydroxybenzoic acid	*(o)*	94
(p)	Anthranilic acid	*(p)*	96
(q)	*m*-Aminobenzoic acid	*(q)*	95
(r)	*p*-Aminobenzoic acid	*(r)*	93
(s)	β-Mercaptopropionic acid	*(s)*	91

[a] Yield of dienol ester.

Even with an excess of *(1)* no reaction occurs with the hydroxyl, amino, or mercapto group. The non-isolable primary adducts *(3)* resist detection by NMR spectroscopy even at −60°C in accord with earlier reports[1,7]. The enol esters *(4)* are stable at room temperature, and generally crystallize readily and resist hydrolysis. On reaction with the Li, Na, and K salts of primary, secondary, and tertiary aliphatic thiols and of thio- and seleno-phenol in tetrahydrofuran at 0°C



(4) *(5)*, X = S; *(6)*, X = Se

Table 2. Synthesis of thiol and selenol esters, *(5)* and *(6)*, from *(4)*.

Enol ester *(4)*	*(5)* and *(6)*		Yield [%] [a]
(b)	*(5b)*	R′=C_6H_5	89
(c)	*(5c)*	R′=C_6H_5	83
(f)	*(5f)*	R′=C_6H_5	72 [b]
(g)	*(5g)*	R′=C_6H_5	91
		R′=C_6H_{11}	79
		R′=$C(CH_3)_3$	84
	(6g)	R′=C_6H_5	88
(h)	*(5h)*	R′=C_6H_5	78
(j)	*(5j)*	R′=C_6H_5	83
(k)	*(5k)*	R′=C_6H_5	89
(r)	*(5r)*	R′=C_6H_5	81

[a] Yields of isolated pure compounds, not optimized. [b] Yield of dithiol ester.

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they rapidly afford the thiol and selenol esters *(5)* and *(6)*, respectively, in good yields (Table 2).

The enol esters *(4b)*, *(4c)*, and *(4f)* of α-hydroxy carboxylic acids are exceptions; their transformation into *(5b)*, *(5c)*, and *(5f)*, respectively, is best accomplished with thiophenol in the presence of 10 mol % of 4-dimethylaminopyridine[8]. The alkali salt of *N*,*N*-dimethylacetoacetamide accompanying *(5)* or *(6)* is easily removed by filtration (or—after neutralization—*N*,*N*-dimethylacetoacetamide is removed by washing with water). Activation with *(1)* and acylation to give *(5)* and *(6)* can be carried out as a one-pot reaction without isolation of *(4)*[9].

Procedure

(*Z*)-*N*,*N*-Dimethyl-3-(3α,7α,12α-trihydroxy-5β-cholanoyloxy)crotonamide *(4j)*: A solution of cholic acid *(2j)* (4.08 g, 10 mmol) in anhydrous THF (20 ml) is added to a stirred solution of *(1)* (1.16 g, 10.5 mmol) in anhydrous THF (30 ml) at −50 °C with exclusion of moisture. After 20 min at −50 °C, the mixture is allowed to warm to room temperature and then evaporated down *in vacuo*. Recrystallization of the residue from chloroform/*n*-hexane gives 5.08 g (98 %) of colorless crystals, m.p. 166—167 °C.

S-Cyclohexanethiol ester of 12-hydroxystearic acid *(5g)*: A solution of Li cyclohexanethiolate (1.28 g, 10.5 mmol) in anhydrous THF (20 ml) is added to a solution of *(4g)* prepared from *(1)* (10.5 mmol) and *(2g)* (10 mmol) in anhydrous THF (50 ml). After 1 h at 0 °C, precipitated Li *N*,*N*-dimethylacetoacetamide is filtered off and the filtrate washed with water after addition of ethyl acetate (100 ml). After drying over $MgSO_4$ and removal of solvent, the residue is dissolved in methylene chloride and filtered over silica gel (Kieselgel 60, Merck). The oil crystallizes on concentration to give 3.14 g (79 %) of colorless crystals, m.p. 37—38 °C.

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(1), 20568-22-3; *(2b)*, 90-64-2; *(2c)*, 1123-28-0; *(2d)*, 79-14-1; *(2e)*, 36413-60-2; *(2f)*, 147-71-7; *(2g)*, 106-14-9; *(2h)*, 540-12-5; *(2i)*, 56-45-1; *(2j)*, 81-25-4; *(2k)*, 156-38-7; *(2l)*, 7400-08-0; *(2m)*, 69-72-7; *(2n)*, 99-06-9; *(2o)*, 99-96-7; *(2p)*, 118-92-3; *(2q)*, 99-05-8; *(2r)*, 150-13-0; *(2s)*, 107-96-0; *(4b)*, 65545-06-4; *(4c)*, 65545-07-5; *(4d)*, 65545-08-6; *(4e)*, 65545-09-7; *(4f)*, 65545-10-0; *(4g)*, 65545-11-1; *(4h)*, 65545-12-2; *(4i)*, 65545-13-3; *(4j)*, 65620-47-5; *(4k)*, 65545-14-4; *(4l)*, 65545-15-5; *(4m)*, 65545-16-6; *(4n)*, 65545-17-7; *(4o)*, 65545-18-8; *(4p)*, 65545-19-9; *(4q)*, 65544-96-9; *(4r)*, 65544-97-0; *(4s)*, 65544-98-1; *(5b)*, R′ = C_6H_5, 65544-99-2; *(5c)*, R′ = C_6H_5, 65545-00-8; *(5f)*, R′ = C_6H_5, 65545-01-9; *(5g)*, R′ = C_6H_5, 61049-79-4; *(5g)*, R′ = C_6H_{11}, 65545-02-0; *(5g)*, R′ = $C(CH_3)_3$, 58587-08-9; *(5h)*, R′ = C_6H_5, 60718-35-6; *(5j)*, R′ = C_6H_5, 65634-38-0; *(5k)*, R′ = C_6H_5, 65545-03-1; *(5r)*, R′ = C_6H_5, 64001-55-4; *(6g)*, R′ = C_6H_5, 65545-04-2; Li cyclohexanethiolate, 65545-05-3

[1] The reagent *(1)* can be conveniently handled in air at room temperature, but is stable for prolonged periods only at −50 °C: *H.-J. Gais, K. Hafner, M. Neuenschwander*, Helv. Chim. Acta *52*, 2641 (1969); references cited therein.

[2] Preparation resembling that by *E. Benary*, Ber. Dtsch. Chem. Ges. *63*, 1573 (1930); *R. Müller, H. Plieninger*, Chem. Ber. *92*, 3009 (1959). We are grateful to Chemische Werke Hüls AG, Marl, for a gift of 4,4-dimethoxy-2-butanone.

[3] a) *R. B. Woodward, R. A. Olofson*, Tetrahedron Suppl. 7, 415 (1966); b) *W. Steglich, G. Höfle, W. König, F. Weygand*, Chem. Ber. *101*, 308 (1968); *A. Niederhauser, G. Bart, M. Neuenschwander*, Helv. Chim. Acta *56*, 2427 (1973); references cited therein.

[4] *(1)* is also capable of addition to alcohols, amines, and thiols, but in most cases only under drastic conditions: a) [1]; b) *A. Niederhauser, A. Frey, M. Neuenschwander*, Helv. Chim. Acta *56*, 944 (1973); c) *H.-J. Gais*, Dissertation, Technische Hochschule Darmstadt 1973.

[5] The ability of enol esters of type $R^1_2N—CO—CR^2{=}CR^3—O—CO—R^4$ to effect acyl transfer largely depends upon the substituents R^1 and R^2: cf. [3b]; *R. B. Woodward, R. A. Olofson, H. Mayer*, Tetrahedron Suppl. *8*, 321 (1966).

[6] The enol esters *(4)* are also very suitable as acyl transfer agents for peptide synthesis: *H.-J. Gais*, unpublished.

[7] Previously described reactions of *(1)* with carboxylic acids are limited to formic, acetic, propionic, butyric, benzoic, and trifluoroacetic acid: [1]; [4c]; *A. Niederhauser, M. Neuenschwander*, Helv. Chim. Acta *56*, 1318 (1973).

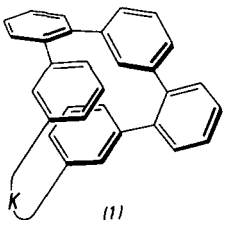
[8] *W. Steglich, G. Höfle*, Angew. Chem. *81*, 1001 (1969); Angew. Chem. Int. Ed. Engl. *8*, 981 (1969). We are grateful to Professor *H. Vorbrüggen*, Schering AG, Berlin, for kindly supplying 4-dimethylaminopyridine.

[9] Correct elemental analyses were obtained for all compounds listed; the IR and NMR data are compatible with the structures.

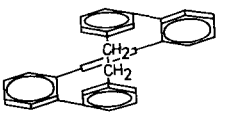
A New Helical Molecular Skeleton [**]

By *Fritz Vögtle* and *Erich Hammerschmidt* [*]

We wish to report a helical sequence of non-annelated aromatic rings *(1)* in which the screw shape of the molecule is imposed by a clamp (*K*) at the ends of a chain made up of five phenylene units[1]:

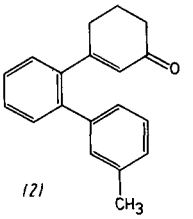


(1)

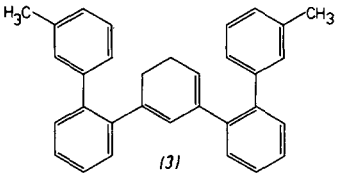


(1a)

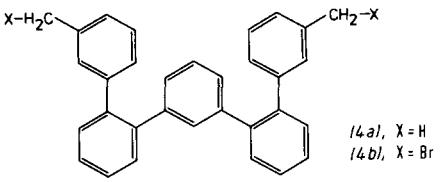
Our strategy for synthesizing this hitherto unknown hydrocarbon with the shortest possible clamp *(1a)* (Table 1) resembles that used by *Woods et al.*[2] for the preparation of the *m*-terphenyl system. 3-Ethoxy-2-cyclohexen-1-one was converted by treatment with 3′-methylbiphenyl-2-lithium or -2-magnesium iodide *via* the intermediates *(2)*, *(3)*, and *(4a)* [dehydrogenation of *(3)* with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone] into the bromide *(4b)* [NBS bromination of *(4a)*], which was smoothly cyclized by the new thioacetamide method[4] under high-dilution conditions[3a] to form the sulfide *(1c)*. Pyrolysis of its sulfone *(1d)* at 500 °C/5×10^{-5} torr gives the hydrocarbon *(1a)*. Reaction of the dibromide *(4b)* with ethane-1,2-dithiolate leads to the cyclic sulfide *(1e)*, whose sulfone *(1f)* likewise affords *(1a)* on pyrolysis[3].



(2)



(3)



(4a), X = H
(4b), X = Br

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

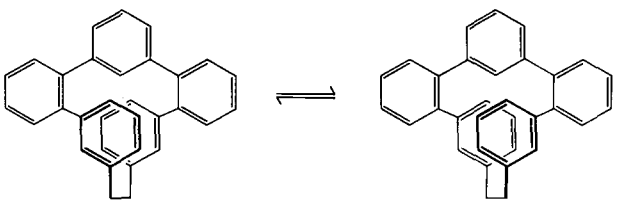
Table 1. Ring systems synthesized; coalescence temperature T_c, and free energies of activation $\Delta G_c^{\neq}$ for the $(P)\rightleftharpoons(M)$ transition.

Cpd. [a]	Clamp K in *(1)*	Yield [%]	M.p. [°C] (Solvent)	T_c [°C]	$\Delta G_c^{\neq}$ [kcal/mol] (kJ/mol)	^{1}H-NMR [b]
(1a)	$-H_2C-CH_2-$	44 (from *(1f)*) 87 (from *(1d)*)	235 (C_6H_6/EtOH)	-70 ± 5	10.5 ± 0.5 (43.9 ± 2)	2.80
(1b)	$-HC=CH-$	47 (from *(1a)*)	237—238 (C_6H_6/EtOH)	[c]	—	6.41
(1c)	$-H_2C-S-CH_2-$	79 (from *(4b)*)	liq.	—	—	3.39
(1d)	$-H_2C-SO_2-CH_2-$	38 (from *(1c)*)	281—282 (glacial acetic acid)	-55 ± 5	11.5 ± 0.5 (48.1 ± 2)	3.94
(1e)	$-H_2C-S(CH_2)_2S-CH_2-$	58 (from *(4b)*)	193—194 (ethyl acetate)	-70 ± 5	10.7 ± 0.5 (44.8 ± 2)	3.54
(1f)	$-H_2C-SO_2(CH_2)_2SO_2-CH_2-$	75 (from *(1e)*)	315 (glacial acetic acid)	[d]	—	—

[a] Composition confirmed by correct elemental analyses and mass spectra.
[b] 80 MHz; in $CDCl_3$ at 35°C; the δ-values apply to the H atoms indicated in the second column of the table.
[c] The compound contains no diastereotopic bridge protons.
[d] Sparingly soluble.

Halogenation and subsequent elimination transforms *(1a)* into the alkene *(1b)* clamped by one CC double bond.

The (temperature dependent) ^{1}H-NMR spectra of the ring systems *(1a)*, *(1b)*, *(1d)*, *(1e)* show the molecules to be helical at low temperatures: the signals of the benzylic CH_2 protons of *(1a)*, *(1d)*, *(1e)* appear as singlets at room temperature but display considerable broadening on cooling[5]. Splitting of this singlet to an AB system can be observed with the sulfone *(1d)* ($T_c\approx-55$°C). Thus, as in the helicenes[1], interconversion between minus (*M*) and plus (*P*) helices is observed, albeit below room temperature:



The ^{1}H-NMR absorption of the terminal *m*-phenylene rings of the alkene *(1b)* are shifted downfield relative to *(1a)*. This is in accord with the widening of the bond angle at the (*Z*)-stilbene group expected for *(1b)* and the consequent increase in the distance between the *m*-phenylene rings.

As in a helical *o*-quaterphenyl skeleton prepared on a former occasion[1,6], the racemization barrier of compounds *(1)* depends upon the nature and the length of the clamp *K*: the sulfone exhibits the highest $(P)\rightleftharpoons(M)$ transition threshold (cf. Table 1).

In the UV spectra, the transition from the open-chain hydrocarbon 3,3''''-dimethyl-1:1',2':1'',3'':1''',2''':1''''-quinquephenyl *(4a)* ($\lambda_{max}=237.5$ nm, $\log\varepsilon=4.73$) to *(1a)* ($\lambda_{max}=234$ nm, $\log\varepsilon=4.67$), and the transition from *(1a)* to *(1b)* ($\lambda_{max}=233$ nm, $\log\varepsilon=4.88$) are accompanied by a hypsochromic shift (in $CHCl_3$)[7]. The former can be explained in accord with the results of *Woods et al.*[2b] for open-chain polyphenylenes by a diminished coplanarity of the rings. In the second case, a reduction of the bathochromic effect appears to prevail, which is due to π-π interactions induced by clamping by the CH_2CH_2 chain as a result of bond angle widening in the stilbene system *(1b)*. In the former case the π-π interactions appear to be overcompensated by biphenyl twisting.

We consider the significance of studies on such new (flexible) helical systems to lie not only in stereochemical parallels to the helicenes and spectroscopic and theoretical interest in helical compounds of varying pitch and number of turns, but above all in the fact that comparison with space filling models provides information about the quality of agreement between such models and the intramolecular dynamic stereochemistry, and especially the flexibility of aromatic rings and structural units. Predictions about such intramolecular processes in the numerous conceivable "phenylen*icenes*"[8] yet to be synthesized are thus facilitated.

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CAS Registry numbers:
(1a), 65879-17-6; *(1b)*, 65879-18-7; *(1c)*, 65879-19-8; *(1d)*, 65879-20-1; *(1e)*, 65879-21-2; *(1f)*, 65879-22-3; *(2)*, 65879-23-4; *(3)*, 65879-24-5; *(4a)*, 65879-25-6; *(4b)*, 65899-40-3; 3-ethoxy-2-cyclohexen-1-one, 5323-87-5; ethane-1,2-dithiolate, 540-63-6

[1] Cf. *F. Vögtle, M. Atzmüller, W. Wehner, J. Grütze*, Angew. Chem. *89*, 338 (1977); Angew. Chem. Int. Ed. Engl. *16*, 325 (1977).
[2] a) *G. F. Woods, I. W. Tucker*, J. Am. Chem. Soc. *70*, 2174 (1948); b) *G. F. Woods, A. L. van Artsdale, F. T. Reed, ibid. 72*, 3221 (1950).
[3] Cf. a) *J. Grütze, F. Vögtle*, Chem. Ber. *110*, 1978 (1977); b) *L. Rossa, F. Vögtle*, Tetrahedron Lett. *1977*, 3577.
[4] *E. Hammerschmidt, W. Bieber, F. Vögtle*, Chem. Ber., in press.
[5] This also applies to some phenylene protons; however, accurate assignment is difficult.
[6] The racemate of the ethano compound *(7o)* described in ref. [1] has meanwhile been shown to crystallize spontaneously as enantiomers. We are indebted to Doz. Dr. *H. Irngartinger*, Heidelberg, for this information.
[7] λ and ε are strongly solvent dependent.
[8] Molecules which form helices not by *ortho* fusing of aromatic rings like hel*icenes* but instead exist as helical conformers as a result of clamping of suitably arranged *o,m,p*-oligophenylene units.

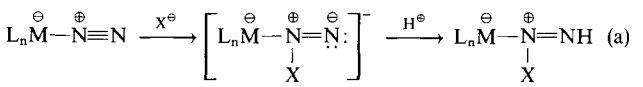
Consecutive Nucleophilic and Electrophilic Attack on N_2 Ligands: Synthesis of Azo Compounds from Molecular Nitrogen[1]

By *Dieter Sellmann* and *Woldemar Weiss*[*]

The catalytic reduction of molecular nitrogen to organic nitrogen compounds under mild conditions is not yet possible. We recently found the reduction of coordinated dinitrogen by bases ($X^{\ominus}$) and subsequent protonation to represent a new reaction of the N_2 molecule[2].

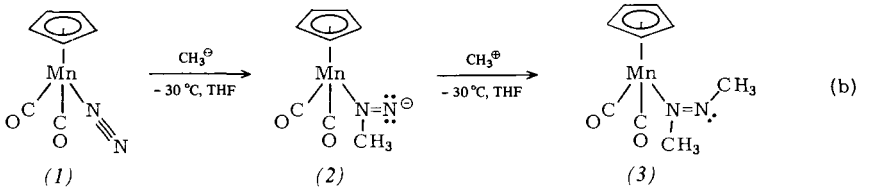
This reaction proceeds at low temperatures and appears to be of fundamental importance with regard to our under-

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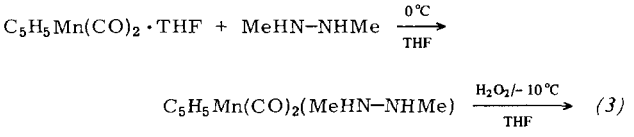


standing of the mechanism and catalysis of N_2 reduction; the reaction steps can be observed separately and the N_2-coordinating metal center is preserved in the course of the N_2 reduction, as has been shown by the reaction of $C_5H_5Mn(CO)_2N_2$ with LiC_6H_5 and H_2SO_4 to give the phenyldiazene complex $C_5H_5Mn(CO)_2[N(C_6H_5)=NH]$[2].

In order to prove the general validity of reaction (a) we have also investigated the nucleophilic addition of alkyl anions with $LiCH_3$. Owing to the instability of alkyldiazene complexes, the addition product formed cannot be detected by subsequent protonation. However, its appearance is unequivocally established by alkylation with methyl cations to yield an azomethane complex.

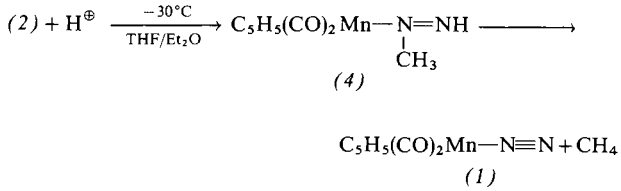


In the first step of reaction (b) the ν_{N_2} and ν_{CO} bands of *(1)* at 2165, 1962, and 1908 cm^{-1} respectively in the IR spectrum disappear while two new ν_{CO} absorptions at 1853 and 1730 cm^{-1} are observed, which we attribute to the adduct *(2)*. In the second step, methylation by $(CH_3)_3OBF_4$ yields complex *(3)*; after chromatography (SiO_2/toluene/−50 °C) and separation from decomposition and by-products, *e.g.* the carbene complex $C_5H_5Mn(CO)_2[C(OCH_3)CH_3]$, *(3)* is isolated as analytically pure red crystals (yield 14 %), which are moderately air- and heat sensitive, soluble in polar as well as nonpolar organic solvents, and may be recrystallized from acetone at 10°/−78 °C. Independent synthesis from *N,N'*-dimethylhydrazine yields an identical product.

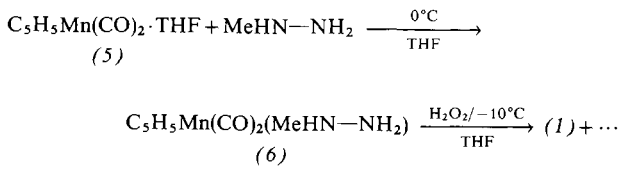


The IR spectrum of *(3)* in acetone shows two ν_{CO} bands of equal intensity at 1925 and 1860 cm^{-1}; in KBr two characteristic ν_{CH} bands are seen at 2998 and 2930 cm^{-1} and an intense $\nu_{N=N}$ band due to the azomethane ligand at 1518 cm^{-1}. The ^{1}H-NMR spectrum (60 MHz, $(CD_3)_2CO$, 36 °C, rel. TMS) shows three signals of the correct intensity at $\delta=4.46$ (C_5H_5 ring) and $\delta=4.18$ and 4.00 (two nonequivalent methyl groups). Hence, the azomethane ligand must be coordinated *via* one nitrogen lone pair and not "side-on", a conclusion which is additionally supported by the strong $\nu_{N=N}$ band in the IR spectrum. In the mass spectrum (42 eV, $T_S=30$ °C) the molecular ion is observed at $m/e=234$; after loss of CO, $[C_5H_5Mn(CH_3N=NCH_3)]^{+\cdot}$ is observed as the first fragment ion.

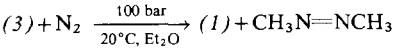
Protonation of the adduct *(2)* with HCl or H_2SO_4 results, even below −30 °C, in violent evolution of gas and regeneration of *(1)*, probably due to



The intermediacy of the methyldiazene complex *(4)* is supported by the reaction of the corresponding methylhydrazine complex *(6)*.

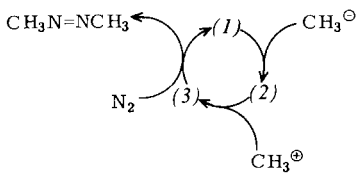


By analogy with the equilibrium[3] *(1)* + THF ⇌ *(5)* + N_2 in tetrahydrofuran solution, a similar equilibrium should also exist between *(1)*, *(3)*, and N_2. Indeed, on applying N_2 pressure to ethereal solutions of the azomethane complex *(3)* the following reaction is observed:



The formation of *(1)* is proved by IR spectroscopy, and that of the azomethane liberated by gas chromatography and mass spectrometry.

Thus, in principle, azomethane can be synthesized catalytically from molecular nitrogen according to the following cycle:



Extensive repetition of this catalytic cycle, however, is impeded by side reactions which destroy the $C_5H_5Mn(CO)_2$ catalyst after a short time.

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[1] Reactions at Complexed Ligands, Part 26. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Dr. Otto Röhm Memorial Foundation.—Part 25: *D. Sellmann, A. Brandl, R. Endell*, Z. Naturforsch., in press.

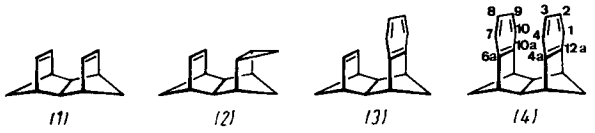
[2] *D. Sellmann, W. Weiss*, Angew. Chem. *89*, 918 (1977); Angew. Chem. Int. Ed. Engl. *16*, 880 (1977).

[3] *D. Sellmann*, Angew. Chem. *84*, 549 (1972); Angew. Chem. Int. Ed. Engl. *11*, 534 (1972).

An Unusual Benzene/Benzene Through-Space Interaction[**]

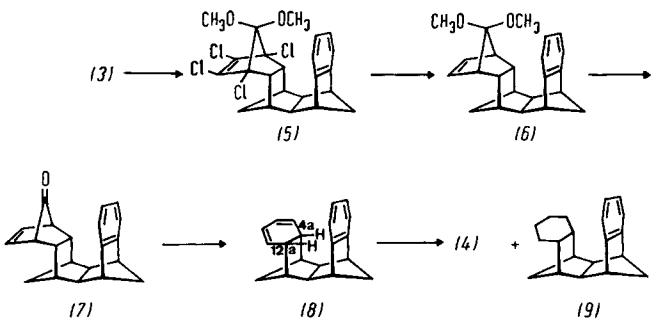
By *Horst Prinzbach, Gottfried Sedelmeier, Carl Krüger, Richard Goddard, Hans-Dieter Martin,* and *Rolf Gleiter*[*]

The β-parameters[1] recently determined on the basis of models for the 1,6-diene *(1)* and its homo-derivative *(2)* would indicate unusual through-space interactions between benzene/ethylene and benzene/benzene moieties in the compounds *(3)* and *(4)*, respectively. We report here on the synthesis and X-ray structure analysis of *(4)* and on the PE spectroscopic investigation of *(3)* and *(4)*.



(1) *(2)* *(3)* *(4)*

We have prepared the hexacyclic compound *(4)*[2] from *(3)*[3] *via* the intermediates *(5)*—*(8)*. Addition of tetrachlorocyclopentadienone dimethyl acetal (*o*-dichlorobenzene, 180 °C, 14 h; m.p. 163—164 °C, 80 %), dehalogenation (Na/*t*-BuOH/tetrahydrofuran, 65 °C, 16 h; m.p. 126—127 °C, 60%), hydrolysis (40% sulfuric acid, CH_2Cl_2, 20 °C, 60 h; m.p. 135 °C, 95 %), and CO-elimination (xylene, 140 °C, 5 h; m.p. 139—140 °C, 65 %) proceed without complication. However, the last step must be carried out under unusual conditions: the sterically shielded hydrogen atoms 4a(12a)-H ($\tau = 8.17$)[4] are eliminated only on heating the mixture of *(8)* and to 250 °C a large excess of 10% Pd/C. Gas-chromatographic separation (10 % SE30, 4 m, 190 °C, He) of the mixture affords *(4)* [m.p. 174—175 °C, 85 %; ^{1}H-NMR ($CDCl_3$): $\tau = 3.55$ (m, 8H), 6.8—7.0 (m, 6H), 8.0 (d, $J = 8.0$ Hz, 2H), 8.23 (d, 2H); ^{13}C-NMR ($CDCl_3$): $\delta = 144.4$, 125.3, 123.5, 59.0, 46.6, 45.9] and *(9)* [m.p. 92—93 °C, 15 %].



Noteworthy, in view of the through-space interaction in *(4)*, is the longwave absorption between 270 and 310 nm ($\varepsilon \approx 300$) in the UV spectrum, which is absent in the case of indan[5] and *(9)*. Very similar effects observed in other compounds were previously ascribed, as in "janusene"[6], to CT transitions.

The geometry of *(4)* was determined by X-ray structure analysis[7a] (Fig. 1): benzene/benzene compression in the molecule is reduced by widening of the angles between the planes I/II (184.7°)[7b], II/III (119.0°), III/IV (133.1°), IV/V (118.4°), and V/VI (183.7°). Thus, the interplanar angle between the two benzene rings is 18.6°; the distances d_1 and d_2 are 3.04 and 3.82 Å, respectively.

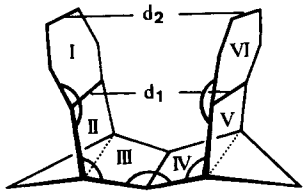


Fig. 1. Crystal structure of the hexacyclic compound *(4)*.

Analysis of the PE spectra of *(3)* ($IP_{i,v} = 8.0$, 8.85, 9.10, 10.0 eV) and the reference compounds *(10)* ($IP_{i,v} = 8.30$, 8.70, 9.60 eV)[8] and *(11)* ($IP_{1,v} = 8.60$, corrected for transannular strain $IP_{1,v}^{corr} = 8.9$ eV[1], gives $H_{i,j}(3) = -0.45$ eV and $\beta(3) = \sqrt{2}H_{i,j} = -0.64$ eV (Fig. 2).

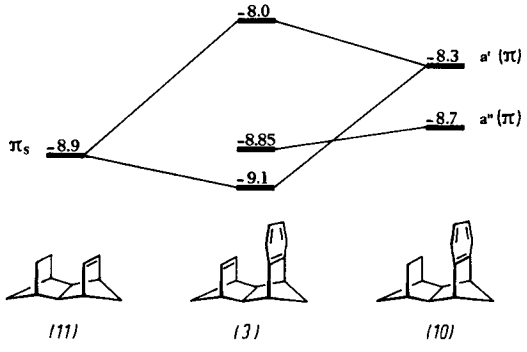


Fig. 2. Orbital correlation diagram for the compounds *(3)*, *(10)*, and *(11)*.

The first four bands in the PE spectrum of *(4)* can be readily reproduced using the basis energies of *(10)* and assuming an average interaction integral of $\beta_{AV} = -0.5$ eV: -7.8 ($b_2(\pi)$), -8.2 ($a_2(\pi)$), -8.8 ($a_1(\pi)$), -9.2 ($b_1(\pi)$) (Fig. 3). This assignment is confirmed by a MINDO/3 calculation[9].

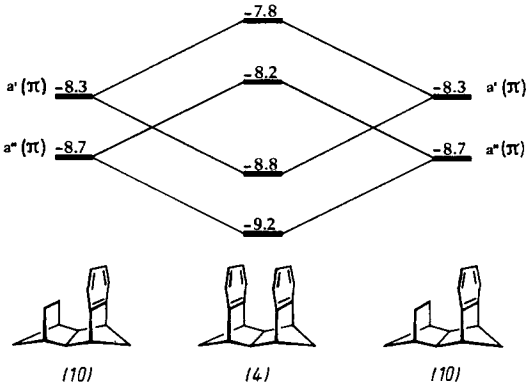


Fig. 3. Energy levels of *(4)* derived from the experimentally determined vertical ionization potentials [eV] of *(10)* using a resonance integral $H_{i,j} = \beta_{AV} = \langle 2p_i/\mathcal{H}/2p_{i'}\rangle = -0.5$ eV.

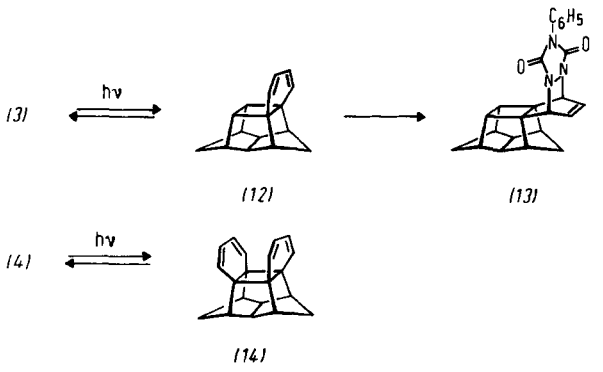
This analysis is based on the assumption that $\langle 2p_i/\mathcal{H}/2p_{i'}\rangle = \beta_{AV}$ for all i 2p(π) atomic orbitals. However,

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on the basis of the structural data of *(4)* (Fig. 1) it would be more realistic to use $\beta' = \beta_{4a,6a} = \beta_{10a,12a} > \beta'' = \beta_{1,10} = \beta_{4,7} > \beta''' = \beta_{2,9} = \beta_{3,8}$. This gives $H_{i,j}(a'(\pi)) = \frac{1}{2}(\beta' + \beta''')$ and $H_{i,j}(a''(\pi)) = \frac{1}{6}(\beta' + 4\beta'' + \beta''')$. Now, using the ratio of the β-parameters corresponding to the ratio of the overlap integrals $\beta' : \beta'' : \beta''' = 3:2:1$ gives $H_{i,j}(a'(\pi)) = H_{i,j}(a''(\pi))$, *i.e.* assumption of an equal average β_{AV} value for $a'(\pi)$ and $a''(\pi)$ is permissible.

At $\beta = -0.5$ eV, *(4)* shows a benzene/benzene interaction comparable with that previously found only in [2.2]paracyclophane ($\beta = -0.5$ to -0.7 eV), in [2.2.2](1,3,5)cyclophane ($-0.4 < \beta \leq -0.7$ eV) and in [2.2]metacyclophane ($\beta \approx -1.2$ eV)[10]. The homoconjugation in *(3)*, with $\beta = -0.64$ eV, is expectedly still more pronounced ($\beta(3) > \beta_{AV}$). According to preliminary photolysis experiments[2], on acetone-sensitized excitation *(3)* undergoes [2+6]-cycloaddition to give *(12)*, and on direct excitation *(4)* undergoes [6+6]-cycloaddition to give *(14)*.



(12) is isolated from the photolysis equilibrium *e.g.* as the *N*-phenyltriazolinedione adduct *(13)* [m.p. 230°C; ^{1}H-NMR (360 MHz, $CDCl_3$): $\tau = 2.5$–2.75 (5H), 2.65 (2H), 4.98 (2H), 7.13 (2H), 7.43 (2H), 7.66 (2H), 7.84 (2H), 8.15, 8.49 (AB, $J = 10$ Hz), 8.26, 8.40 (AB, $J = 10$ Hz)].

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(3), 3647-99-2; *(4)*, 65879-09-6; *(5)*, 65879-02-9; *(6)*, 65879-03-0; *(7)*, 65879-04-1; *(8)*, 65879-05-2; *(9)*, 65879-06-3; *(10)*, 3648-04-2; *(11)*, 1076-12-6; *(12)*, 65879-07-4; *(13)*, 65899-39-0; *(14)*, 65879-08-5; tetrachlorocyclopentadienone dimethyl acetal, 2207-27-4; *N*-phenyltriazolinedione, 4233-33-4

[1] *H. Prinzbach, G. Sedelmeier, H.-D. Martin*, Angew. Chem. *89*, 111 (1977); Angew. Chem. Int. Ed. Engl. *16*, 103 (1977); *H.-D. Martin, R. Schwesinger*, Chem. Ber. *107*, 3143 (1974).

[2] *G. Sedelmeier*, Dissertation, Universität Freiburg 1978.

[3] *K. Mackenzie*, J. Chem. Soc. *1965*, 4646.

[4] Cf. *O. Ermer*, Angew. Chem. *89*, 833 (1977); Angew. Chem. Int. Ed. Engl. *16*, 798 (1977).

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[6] *S. J. Christol, D. C. Lewis*, J. Am. Chem. Soc. *89*, 1476 (1967); *W. M. Macintyre, A. H. Tench*, J. Org. Chem. *38*, 130 (1973).

[7] a) Crystallographic data: $a = 9.8991(4)$, $b = 12.3169(5)$, $c = 12.8885(4)$ Å, $\alpha = 118.471(3)$, $\beta = 91.603(4)$, $\gamma = 91.089(3)°$, $Z = 4$, space group $P\bar{1}$, $R = 0.052(R' = 0.069)$, 3619 observed reflections ($I \geq 2\sigma(I)$); atomic parameters and F_o/F_c lists are available on request from the authors (C. K.).—b) Mean values for the two independent molecules in the asymmetric unit are given.

[8] The analysis of *(10)* corresponds to those of other disubstituted benzenes, cf. *F. Brogli, E. Giovannini, E. Heilbronner, R. Schurter*, Chem. Ber. *106*, 961 (1973).

[9] MINDO/3 calculation [eV]: -8.04 ($b_2(\pi)$), -8.56 ($a_2(\pi)$), -8.75 ($a_1(\pi)$) and -9.18 ($b_1(\pi)$).

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Aluminum Tris(dihydrogen Phosphate)[**]

By *Rüdiger Kniep* and *Michael Steffen*[*]

The Al_2O_3—P_2O_5—H_2O system contains several ternary (actually quasiternary) orthophosphates; depending upon the $Al_2O_3 : P_2O_5$ ratio they are respectively designated as acidic (< 1), neutral ($= 1$), or basic (> 1) aluminum phosphate hydrates (APH's). Basic and neutral APH's occur as minerals; the aqueous solutions of acidic phases are commonly used as inorganic binders[1]. While the variety of crystalline basic and neutral APH's has already been extensively established by crystal structure analyses[2], identification of the crystalline acidic phases has been limited mainly to studies of the system at variable temperatures[3]. $Al(H_2PO_4)_3$ is the longest known[4] acidic APH and is now also the first phase of this group of compounds to have its crystal structure elucidated.

$Al(H_2PO_4)_3$ crystallizes as ditrigonal prisms (up to several cm in length) on evaporation of viscous solutions (formation of aggregation polymers[5]) of aluminum in concentrated phosphoric acid (Al:P = 1:5) at 50°C. The crystals are strongly hygroscopic and melt at 243°C (DTA). They were sealed in glass capillaries for the X-ray investigation.

The structure[6] is made up of isolated AlO_6 octahedra stacked with corner sharing $O_2P(OH)_2$ tetrahedra to form "columns" $^1_\infty[Al(H_2PO_4)_3]_n$ parallel to the crystallographic *c* axis (Fig. 1a). These "columns" are linked together by hydrogen bonds (cf. also Fig. 1b); each OH group acts simultaeously as a proton donor and a proton acceptor.

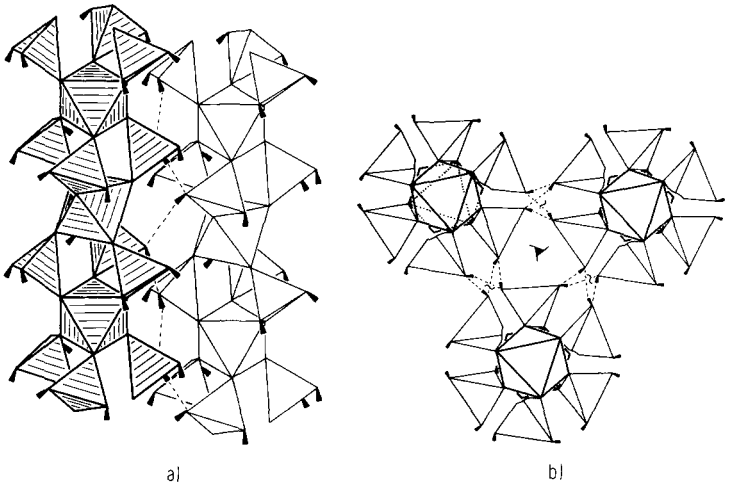


Fig. 1. a) Two structural units $[Al(H_2PO_4)_3]_n$ in a polyhedral representation with intermolecular hydrogen bonds (dashed lines); one such unit is emphasized by hatching. b) Section from the crystal structure of $Al(H_2PO_4)_3$ viewed along one of the threefold screw axes (hydrogen bonds shown as dashed lines).

Principal (averaged) distances [Å] and angles [°]:

Al—O	1.884(2)	O—Al—O	89.8(1)
P—O	1.535(2)	O—P—O	109.3(1)
P—OH	1.579(3)	HO—P—O	107.5(1)
O—H	0.83(5)	HO—P—OH	105.9(1)
H...OH	1.92(5)	O—H...OH	163(4)

Interestingly, the heavy atoms alone appear to form an almost centrosymmetric structure which is rendered significantly acentric only by the orientation of the protons (cf. Fig. 1a: all the protons are directed "downwards").

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By use of the Guinier-Simon technique, a phase transition is shown to take place in $Al(H_2PO_4)_3$ at 60 °C; the very slight change of the powder diagram suggests that this change is due to proton reorientation. Since the structure is acentric and also contains a polar axis, ferroelectricity should be possible.

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CAS Registry numbers:
$Al(H_2PO_4)_3$, 13530-50-2

[1] *J. H. Morris, P. G. Perkins, A. E. A. Rose, W. E. Smith*, Chem. Soc. Rev. 6, 173 (1977).
[2] *P. B. Moore, T. Araki*, Am. Mineral. 59, 974 (1974); *R. Kniep, D. Mootz, A. Vegas*, Acta Crystallogr. *B33*, 263 (1977); references cited therein.
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[6] 969 symmetry-independent reflections ($Mo_{K\alpha}$, Syntex $P2_1$ four-circle diffractometer); 937 reflections were significant ($FO > 3\,\sigma_F$). The structure was solved with the Syntex E-XTL program system: $R = 2.9\,\%$; rhombohedral (R3c), $a = 13.727(5)$, $c = 9.152(1)$ Å, $Z = 6$, $d_{calc.} = 2.12$, $d_{exp.} = 2.10\,g\,cm^{-3}$. The positions of the protons could be established in a difference Fourier synthesis.

An Arsinidene as a Cubane-Type Structural Unit: Synthesis and Structure of $[(CO)_3Fe—AsCH_3]_4$[**]

By *Erika Röttinger* and *Heinrich Vahrenkamp*[*]

The phosphinidene and arsinidene groups RP and RAs are isoelectronic with the sulfur and selenium atoms, respectively, suggesting that there should be some structural relationship between the transition metal complexes having RP and RAs, on the one hand, and S and Se, on the other, as bridging ligands. This is the case for some complexes with metal-metal bonds[1], but not for others. Thus there are still no chalcogen analogs of the dinuclear μ_2-phosphinidene and μ_2-arsinidene complexes described by *Huttner et al.*[2], and the large number of complexes having a cubane skeleton of four metal and four sulfur atoms[3] have no RP or RAs counterparts. We are confident that expected analogies will be substantiated by directed syntheses and now report the Fe_4As_4-cubane *(1)* as a relevant example.

The thermolability of the As—H bond in complexes[4] was utilized in the production of complexed μ_3-methylarsinidene in *(1)*. The stoichiometric Fe:As ratio was already present in the starting complex $(CO)_4Fe \cdot CH_3AsH_2$, which decomposes slowly at room temperature, and rapidly on heating, to form *(1)*. The appearance of only two IR bands in the CO region (2025 (s) and 1985 (m) cm^{-1}) reveals the iron atoms of product *(1)* to have C_{3v} symmetry, and a singlet in the ^{1}H-NMR [$\delta = 1.32$ rel. TMS internal (in benzene)] shows the four arsenic atoms to be equivalent. The molecular ion appears at very low intensity in the FD mass spectrum, the principal fragment being $[(CO)_3Fe—AsCH_3]_2^+$. Compound *(1)* crystallizes from benzene/cyclohexane mixtures as $[(CO)_3Fe—AsCH_3]_4 \cdot 0.75\,C_6H_{12}$, which was used for a structural determination[5].

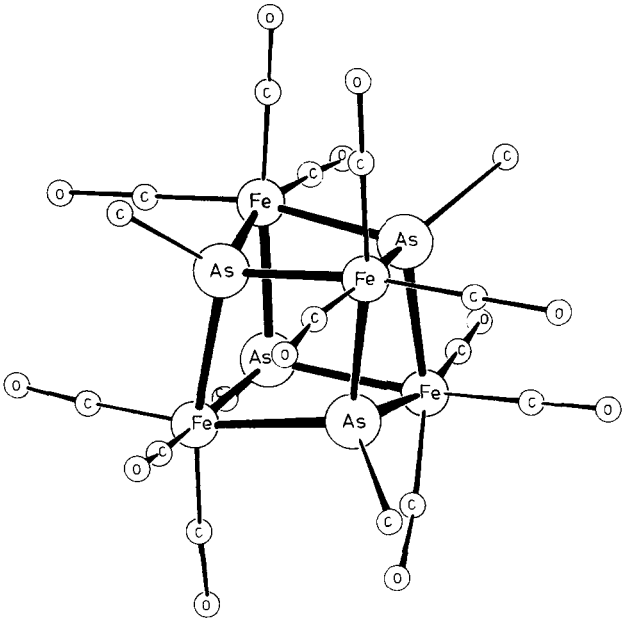


Fig. 1. Molecular structure of tetra-μ_3-methylarsanediyltetrakis(tricarbonyliron) *(1)*.

The molecules of *(1)* (cf. Fig. 1) are located on threefold axes in the crystal. In contrast to the comparable complexes $[(CO)_3Re—SCH_3]_4$[6], $[(CO)_3Os—O]_4$[7], and $[(CO)_3Co—Sb]_4$[8], they thus have the maximum possible symmetry. Like the other complexes, *(1)* also exhibits approximate non-crystallographic T_d-$\bar{4}3m$ symmetry and a distortion of the cubane skeleton arising from the tendency of the $M(CO)_3$ units to adopt octahedral geometry and the main group element units to assume tetrahedral geometry. The angles at iron and arsenic are accordingly $75.9 \pm 0.1°$ and $102.6 \pm 0.2°$, respectively. The Fe—As bond lengths of 241.1 ± 0.5 pm are normal, no metal-metal bonding occurring according to the 18-electron rule.

The Fe_4As_4-cubane *(1)* warrants particular attention on account of the analogy with Fe_4S_4 cubanes. It is our aim to reproduce their varied chemistry[3] by preparative and electrochemical reactions with *(1)*.

Procedure

A solution of CH_3AsH_2 in benzene (10 ml, 1.5 M) is added to a suspension of $Fe_2(CO)_9$ (1.82 g, 5.0 mmol) in benzene (70 ml) and the mixture stirred until all the $Fe_2(CO)_9$ has dissolved and the formation of $(CO)_4Fe \cdot CH_3AsH_2$ can be detected by NMR spectroscopy (1 d). Complete conversion into *(1)* is accomplished by refluxing for 4 h. Removal of solvent and recrystallization from *n*-hexane affords crude *(1)* (960 mg, 83 %) containing varying amounts of solvent. Crystals of homogeneous composition are obtained by column chromatography (4 × 50 cm) with cyclohexane on silica gel and subsequent recrystallization from cyclohexane/benzene.

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(1), 65815-63-6; $Fe_2(CO)_9$, 15321-51-4; CH_3AsH_2, 593-52-2

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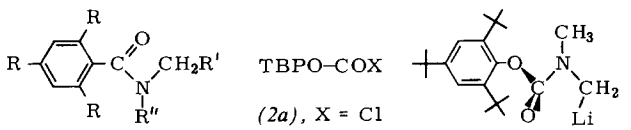
[1] *L. Marko, B. Marko*, Inorg. Chim. Acta *14*, L 39 (1975); *R. C. Ryan, L. F. Dahl*, J. Am. Chem. Soc. 97, 6904 (1975); *G. Huttner, G. Mohr, A. Frank, U. Schubert*, J. Organomet. Chem. *118*, C 73 (1976); *M. Jacob, E. Weiss, ibid. 131*, 263 (1977).
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[3] *H. Vahrenkamp*, Angew. Chem. *87*, 363 (1975); Angew. Chem. Int. Ed. Engl. *14*, 322 (1975).
[4] *P. Umland, H. Vahrenkamp*, Chem. Ber. *110*, 2809 (1977).
[5] The cubic unit cell of these crystals contains eight heterocubane and six cyclohexane molecules: $P\bar{4}3n$, $a = 1873(1)$ pm; 717 independent reflections, solution of structure with MULTAN program, $R = 0.051$.
[6] *W. Harrison, W. C. Marsh, J. Trotter*, J. Chem. Soc. Dalton Trans. *1972*, 1009.
[7] *D. Bright*, Chem. Commun. *1970*, 1169.
[8] *A. S. Foust, L. F. Dahl*, J. Am. Chem. Soc. *92*, 7337 (1970).

2,4,6-Tri-*tert*-butylphenoxyl (TBPO) as Sterically Active Carbonyl-Protecting Group—A New Nucleophilic Dimethylaminomethylating Reagent

By *Dieter Seebach* and *Tillmann Hassel*[*]

Given adequate steric protection[1] of the carbonyl group of amides such as *(1)*, it proves possible to accomplish their deprotonation at the α-*N*—CH_3 and —CH_2 groups with strong bases such as *sec*-butyllithium[1,2]. Organolithium derivatives accessible in this way can only be designated as nucleophilic aminoalkylating reagents if the products obtained with electrophiles can be cleaved to give amines. We have now found this condition to be fulfilled by the 2,4,6-tri-*tert*-butylphenoxyl group (TBPO) in the *N*,*N*-dimethylcarbamate *(2b)* in which the carbonyl C atom has been displaced from the two protecting *o*,*o'*-*tert*-butyl groups by an oxygen in comparison with *(1)*.



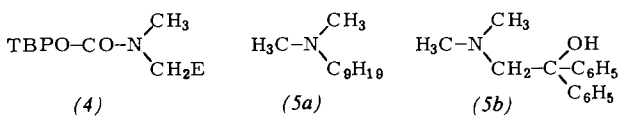
(1), R = C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$

TBPO–COX

(2a), X = Cl

(2b), X = $N(CH_3)_2$

(3)



(4)

(5a)

(5b)

Reaction of tri-*tert*-butylphenol and phosgene[3] gives the chlorocarbonate *(2a)* (*ca.* 50 %) which quantitatively affords *(2b)* (m.p. 121 °C) on treatment with two mol. equiv. of dimethylamine[3]. On stirring of a cooled (ice bath) solution of *(2b)* and tetramethylethylenediamine (TMEDA) (0.1 M in each reagent) in tetrahydrofuran for 90 min with *sec*-butyllithium (10 % excess) quantitative formation of a clear colorless solution of the lithium compound takes place, according to ^{1}H-NMR analysis of a deuterolyzed sample. Compound *(3)* reacts with alkyl halides and aldehydes or ketones to give the carbamates *(4)* of the higher amines *(4a—d)* and amino alcohols *(4e—h)* in the yields listed in Table 1 (recrystallized or chromatographed analytically pure products). The structures *(4)* are confirmed by IR and ^{1}H- and ^{13}C-NMR spectra. Cleavage of the carbamates *(4)* to tertiary amines *(5)* can be accomplished with lithium tetrahydridoaluminate in boiling dioxane; the reaction can be carried out with the crude products *(4)* [*(4b)* pure, gives *(5a)*[4], 51 % after 24 h, 75 % conversion; *(4h)* crude, gives *(5b)*[5], 68 % based on *(2b)* after 6 h].

Table 1. Carbamates *(4)* prepared by reaction of the lithium compound *(3)* with electrophiles.

Electrophile	E in product	*(4)*	Yield [%]	M.p. [°C]
Iodomethane	CH_3	*(4a)*	71	78—79
1-Iodooctane	n-C_8H_{17}	*(4b)*	87 [a]	Oil [a]
Benzyl bromide	$CH_2C_6H_5$	*(4c)*	35 [b]	132
2-Iodopropane	$CH(CH_3)_2$	*(4d)*	32	61—63
Hexanal	CH(OH)-n-C_5H_{11}	*(4e)*	80	111—112
Cyclohexanone	$C(OH)(CH_2)_5$	*(4f)*	63	150
Benzaldehyde	$CH(OH)C_6H_5$	*(4g)*	50 [b]	128
Benzophenone	$C(OH)(C_6H_5)_2$	*(4h)*	61 [c]	122

[a] See the conversion into the known CH_3I adduct of *(5a)*. [b] Not optimized. [c] Cf. higher yield of *(5b)* obtained without purification of *(4h)*.

The TBPO carbonyl group is a regenerable[6] group for acidification of amines[1], and is readily accessible from commercially available materials. The lithium compound *(3)* acts as a $(CH_3)_2NCH_2^{\ominus}$ synthon on cleavage to tertiary amines such as *(5)*[7]. Other cleavage reactions are possible, and other amines can be used.

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(2a), 4511-21-1; *(2b)*, 65832-33-9; *(3)*, 65832-34-0; *(4a)*, 65832-35-1; *(4b)*, 65832-36-2; *(4c)*, 65832-37-3; *(4d)*, 65832-28-2; *(4e)*, 65832-29-3; *(4f)*, 65832-30-6; *(4g)*, 65832-31-7; *(4h)*, 65832-32-8; *(5a)*, 17373-27-2; *(5b)*, 5612-62-4; tri-*t*-butylphenol, 732-26-3; phosgene, 75-44-5; iodomethane, 74-88-4; 1-iodooctane, 629-27-6; benzyl bromide, 100-39-0; 2-iodopropane, 75-30-9; hexanal, 66-25-1; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7; benzophenone, 119-61-9

[1] *R. Schlecker, D. Seebach*, Helv. Chim. Acta *60*, 1459 (1977); *R. Schlecker, D. Seebach, W. Lubosch, ibid. 61*, 512 (1978); references cited therein.
[2] *P. Beak, B. G. McKinnie, D. B. Reitz*, Tetrahedron Lett. *1977*, 1839; *P. Beak, B. G. McKinnie*, J. Am. Chem. Soc. *99*, 5213 (1977).
[3] The phenol is first treated with NaH in tetrahydrofuran and then, in the presence of a trace of dimethylformamide, with 1.1 mol. equiv. of phosgene (toluene solution). [Production of *(2a)* without base: *C. W. Stephens*, US-Pat. 3211774; Chem. Abstr. *64*, P 655f (1966).] After filtration, concentration, dissolution in diethyl ether, and reaction with dimethylamine the product is worked up in aqueous medium and *(2b)* separated from unreacted phenol by filtration over silica gel.
[4] As methiodide, m.p. 168 °C [*H. King, T. S. Work*, J. Chem. Soc. *1942*, 402: 170 °C].
[5] As hydrochloride, m.p. 235 °C [*E. Eidebenz*, Arch. Pharm. *280*, 48 (1942): 234 °C].
[6] The phenol can be recovered quantitatively on $LiAlH_4$ cleavage *(4)* → *(5)*.
[7] Cf. *D. J. Peterson*, Organomet. Chem. Rev. *A 7*, 295 (1972); *D. Seebach, K.-H. Geiss*, J. Organomet. Chem. Library 1, Elsevier, Amsterdam 1976, pp. 1—92 and references cited therein.

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Reactivity of a Sulfonium Ion in Layer Silicates of Montmorillonite Type

By *Jürgen Gosselck* and *Ingfried Stahl*[*]

The intercalation of organic compounds in layer silicates has been known for a long time. Both neutral molecules and organic cations—including sulfonium ions[1]—can be intercalated[2]. We have now examined the reactivity of a

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R_3S^+ ion incorporated into Na-bentonite—a layer silicate of montmorillonite type[3]—and compared it with that of the free salt.

In order to ensure that the reactions do indeed take place *within* the layers we incorporated the *S*-benzyltetrahydrothiophenium ion as a fixed reactant and allowed it to act upon uncharged organic molecules of known intercalating ability. This cation was selected because a sample of bentonite charged therewith was found to give tetrahydrothiophene almost quantitatively by thermal fragmentation on heating to 220 °C. With ethanol as trapping reagent for the benzyl cation suspected as intermediate, we obtained the corresponding benzyl ether. On reaction with arenes in excess (glass autoclave, 220 °C, 12 h) benzyl derivatives were formed in good yields in all cases (Table 1). Under similar conditions but in the absence of Na-bentonite, *S*-benzyltetrahydrothiophenium bromide does *not* react with arenes.

Table 1. Reactions of *S*-benzyltetrahydrothiophenium-bentonite with benzene and benzene derivatives.

Reactant	Products	Overall yield [%]	T [°C]	t [h]
Benzene	Diphenylmethane	60	220	12
		72	220	24
Toluene	*o*- and *p*-Tolyl-phenylmethane [a]	35	220	4
Anisole	*o*- and *p*-Methoxyphenylphenylmethane [b]	85	220	12
		73	220	12
Chlorobenzene	*o*- and *p*-Chlorophenylphenylmethane [c]	37	220	12
Bromobenzene	*o*- and *p*-Bromophenylphenylmethane [d]	40	220	12
p-Xylene	Xylylphenylmethane	77	220	12

[a] Ratio of *ortho* to *para* compound as determined by gas chromatography and ^{1}H-NMR spectroscopy—40:60; [b] 38:62; [c] 32:68; [d] 33:67.

Incorporation of the *S*-benzyltetrahydrothiophenium ion into Na-bentonite from aqueous solutions of the bromide can be accomplished at pH 6.5—7. The basal spacing of the treated bentonite after drying to constant weight at 130 °C/0.05 torr is 14.25 Å as against the original value of 10.1 Å[4].

The exchange capacity of bentonite was determined by stirring defined amounts of dissolved sulfonium salt and bentonite together for 45 min; after filtration and washing, the unconsumed sulfonium salt was determined as the sulfonium reineckate. The yields listed in Table 1 are based on an exchange capacity of 66.5 mmol of $[(CH_2)_4SCH_2C_6H_5]^+$/100 g of Na-bentonite.

Since the presence of bromide ions was ruled out by analytical studies on the bentonite charged with sulfonium ion (Na_2CO_3 extraction)—*e. g.* on the basis of adsorption effects—the reactions must be cationoid and proceed within the layers. The 001 interferences of the reacted bentonites show that the layer structures are largely preserved. After reacting once, the bentonite still exhibited *ca.* 50 % of its original exchange capacity (31.3 mmol/100 g). After recharging, it reacted once again with arenes to give equally high yields.

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[1] *J. W. Jordan*, US-Pat. 2531440 (1950); *E. A. Hauser*, US-Pat. 2531812 (1950).

[2] Survey: *A. Weiss*, Angew. Chem. *75*, 113 (1963); Angew. Chem. Int. Ed. Engl. *2*, 134 (1963); *U. Hofmann, ibid. 80*, 736 (1968) and *7*, 681 (1968), resp.; *G. Lagaly, ibid. 88*, 628 (1976) and *15*, 575 (1976), resp.; *S. L. Swartzen-Allen, E. Matijevic*, Chem. Rev. *74*, 385 (1974).

[3] Supplied by the Erbslöh Company, D-6220 Geisenheim (Germany). We are grateful for a gift of this chemical.

[4] We are indebted to the Inorganic Chemistry Section (Prof. Dr. *Seifert*), for recording the X-ray interference diagrams.

Hexafluorophosphate of the Bis(naphthalene) Radical Cation

By *Heinz P. Fritz, Helmut Gebauer, Peter Friedrich*, and *Ulrich Schubert*[*]

In conjunction with studies on the radical intermediates of anodic substitution reactions we have now obtained red-violet needles of approximate composition $(C_{10}H_8)_2PF_6$ in current yields up to 60 % at platinum electrodes in the electrolyte system CH_2Cl_2/0.02 M Bu_4NPF_6, containing naphthalene in 0.01 M concentration, at −45 °C in an undivided cell at voltages of 10−8 V and current densities of 0.5—2 mA cm^{-2} within 16 h. The chisel-tip shaped crystals can be washed with cold dichloromethane and dried in a high vacuum, but persistently give C values that are too low. They decompose at 65 °C in a sealed tube and on exposure to air smell strongly of naphthalene, which is liberated (visible under a microscope). The mass spectrum exhibits signals for naphthalene, PF_4^+, and binaphthyl, suggesting a possible reaction path of this radical cation salt.

The X-ray structure analysis[1] of the salt $(C_{10}H_8)_2PF_6$ commands particular interest. Apart from confirming the composition, it should reveal what interactions are responsible for the stabilization of the radical cations in the crystal. We found that the naphthalene units are stacked parallel to the *c* axis of the tetragonal unit cell (cf. Fig. 1). Successive $C_{10}H_8$ units are mutually twisted by 90°; the axis of rotation passes through the center of the molecule. The distance between the naphthalene planes of 320 pm is the smallest yet found between arene rings (van der Waals distance of aromatic compounds 340 pm[2], graphite 335 pm, ferrocene 325 pm) and indicates pronounced interaction between the π-electron systems. The interstices between four stacks of naphthalene units are occupied by PF_6^- ions in such a manner that they are surrounded by four $C_{10}H_8$ molecules as nearest neighbors, the naphthalene planes and one octahedral plane being parallel

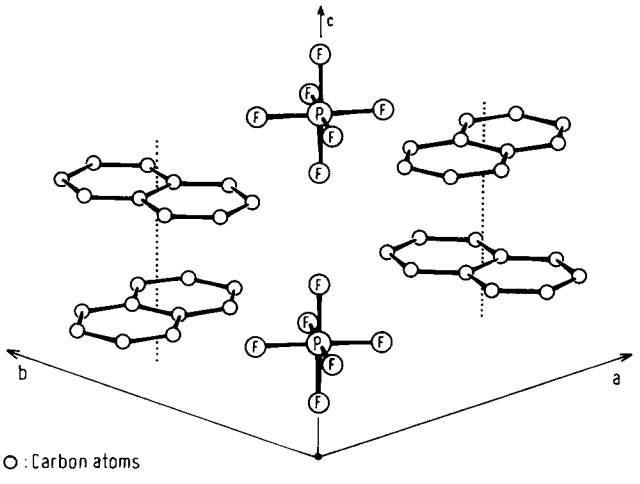


Fig. 1. Contents of a unit cell of $(C_{10}H_8)_2PF_6$. The P atoms are sited on the diagonals of the unit cell, and the centroids of the naphthalene systems on straight lines parallel to the *c* axis.

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to one another. The shortest distances between anions and cations are F···H distances of 251 pm (sum of the van der Waals radii 255 pm[2]).

$(C_{10}H_8)_2PF_6$ has the first proven columnar structure of hydrocarbon units with precise stacking.

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[1] 355 structure factors ($I \geq 3\sigma$, Syntex $P2_1/XTL$, $\sin\theta/\lambda = 0.5043$, $\lambda = 71.069$ pm), $R = 0.048$; tetragonal, space group $P4_2/n$, $Z = 2$, $a = b = 1156(2)$, $c = 640(1)$ pm, $V = 855 \cdot 10^6$ pm^3.

[2] *L. Pauling:* The Nature of the Chemical Bond. Cornell University Press, Ithaca.

Tris[(*N,N,N',N'*-tetramethylethylenediamine)-lithium]hexamethylerbate(III) and -lutetate(III)[1]

By *Herbert Schumann* and *Jochen Müller*[*]

Alkyl-transition metal compounds can be stabilized by the presence of complexing bases and by formation of peralkylated "ate" complexes. Thus *Wilkinson et al.* recently showed that alkyl compounds of uranium are accessible by the latter approach[2], and *Lappert et al.* succeeded in preparing lanthanoid complexes of the type $[LiL_4][M(CH_2SiMe_3)_4]$[3]. While aryl compounds such as $Li[LaPh_4]$[4] or $[Li(thf)_4][Lu(C_6H_3Me_2)_4]$[5] have also been known for some time, the synthesis of peralkyl derivatives has so far been beset with insurmountable difficulties.

Using *N,N,N',N'*-tetramethylethylenediamine (tmen) as a stabilizing base, it has now proved possible to synthesize the first peralkylated complexes of the lanthanoid series containing only methyl ligands. Dropwise addition of an ethereal solution of methyllithium to a suspension of erbium trichloride or lutetium trichloride in diethyl ether and a stoichiometric amount of the diamine affords good yields of the reaction products $[Li(tmen)]_3[ErMe_6]$ and $[Li(tmen)]_3[LuMe_6]$, as analytically pure, pink or white crystals which can be freed from excess methyllithium by recrystallization:

$$MCl_3 + 6\ LiCH_3 + 3\ tmen \xrightarrow[-3\ LiCl]{} [Li(tmen)]_3[M(CH_3)_6]$$

M = Er, Lu; tmen = $(CH_3)_2NCH_2CH_2N(CH_3)_2$

The new compounds are extremely sensitive to air and moisture; however, they exhibit surprising thermal stability and decompose only slowly at their melting point of 138 to 139 °C (M = Er) and 141 to 142 °C (M = Lu). Hydrolysis and alcoholysis expectedly liberate 6 mol of methane (CH_3D on reaction with D_2O) per mol of lanthanoid (detected by gas analysis). The IR spectra show mainly the bands of the coordinated diamine; Raman spectra could not be recorded, even at −100 °C, owing to decomposition of the complexes in the laser beam; no structural information could be obtained for the paramagnetic erbium compound by NMR spectroscopy. However, the ^{1}H-NMR spectrum of the diamagnetic lutetium compound (complete 4f shell) shows a singlet for the methyl groups bound to lutetium at $\delta = -1.18$ rel. TMS in addition to the peaks of tetramethylethylenediamine ($\delta CH_2 = 2.30$, $\delta CH_3 = 2.23$).

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Experimental

A suspension of methyllithium (75.1 mmol) in diethyl ether (60 ml) is added dropwise over 1 h to a suspension of $ErCl_3$ or $LuCl_3$ (11.5 mmol) in ether (60 ml) and *N,N,N',N'*-tetramethylethylenediamine (34.5 mmol) at room temperature. After 2 hours' stirring, LiCl is filtered off and most of the compound, which is only moderately soluble in ether, is washed out of the residue (3 × 50 ml Et_2O). The combined ethereal solutions are concentrated to $^1/_3$ of their volume, whereupon part of the product precipitates. Precipitation is completed at −30 °C and the precipitate filtered off at that temperature. Recrystallization (Et_2O/−30 °C) affords $[Li(tmen)]_3[ErMe_6]$ or $[Li(tmen)]_3[LuMe_6]$ in 30 to 40 % yield.

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[1] Organometallic Compounds of the Lanthanoids, Part 5. This work was supported by the Fonds der Chemischen Industrie and the Senator für Wirtschaft des Landes Berlin (ERP-Sondervermögen, Projekt 2327).— Part 4: *H. Schumann, J. Müller*, J. Organomet. Chem. *146*, C 5 (1978).

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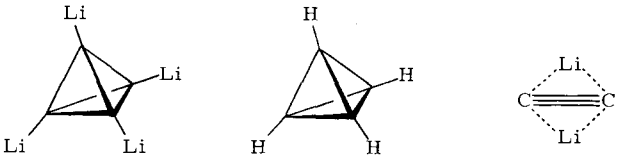
[4] *F. A. Hart, A. G. Massey, M. S. Saran*, J. Organomet. Chem. *21*, 147 (1970).

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C_4Li_4, Tetralithiotetrahedrane?

By *Gerhard Rauscher, Timothy Clark, Dieter Poppinger*, and *Paul von Ragué Schleyer*[*]

Dill pointed out that the strain in small-ring cycloalkanes should be relieved by σ-donating, π-accepting substituents, and hence suggested that tetralithiotetrahedrane *(1)* should be a relatively stable species[1]. We now present a report summarizing our progress towards the realization of this suggestion. In view of the interest in the tetrahedrane problem and numerous synthetic failures[2], our results, although not definitive, are encouraging.



(1) *(2)* *(3)*[4]

C–C 1.538 Å, C–Li 1.829 Å calc.

C–C 1.473 Å, C–H 1.069 Å calc.[3]

Both theoretical and experimental approaches have been employed. When a 0.01 M solution of dilithioacetylene *(3)*[4, 5] in liquid ammonia is irradiated at −45 °C for 6 h with a high pressure mercury lamp, the original C_2Li_2 ^{13}C-NMR peak at $\delta = 75.0$ disappears and is replaced by a singlet at $\delta = 57.2$. This position, which is consistent with the expected sp hybridization of a tetrahedrane carbon[2], does not shift in dimethylformamide solution. Evaporation of the ammonia yields a solvent-free microcrystalline powder[6] which is stable

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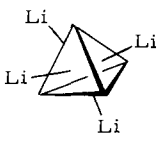
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under argon at −20°C, but decomposes slowly at room temperature. In a mull or in solution in ammonia or dimethylformamide, the product gives IR and Raman spectra quite different from those of C_2Li_2. A chemical reaction definitely has taken place, but hydrolysis of the product gives acetylene in quantitative yield. Although trimers like hexalithiobenzene or hexalithioprismane would give but a single ^{13}C-NMR resonance, the following evidence favors dimers based on tetralithiotetrahedrane or tetralithiocyclobutadiene instead: In field desorption mass spectra[7] only peaks at $m/e=76$ ($C_4{}^7Li_4$) and 75 ($C_4{}^6Li^7Li_3$) were found. Within the inherent limitations of the method, the isotopic ratio agreed with theory. No peaks corresponding to $[C_2Li_2]_n^+$, $n=1$, $n\geq 3$, were observed. Dilithioacetylene did not give the $m/e=76$ and 75 peaks, but ions of $m/e=38$ and 37 were observed instead. We conclude that irradiation of *(3)* gives the dimer C_4Li_4.

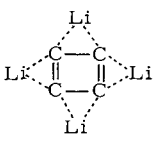
$$2C_2Li_2 \xrightarrow[NH_3]{h\nu} C_4Li_4 \xrightarrow[(\approx 100\,\%)]{H_2O} 2C_2H_2$$

$\delta(^{13}C)=75.0$ $\qquad$ $\delta(^{13}C)=57.2$

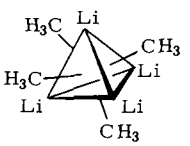
What is the structure of C_4Li_4? Although we hope to solve this question experimentally, *ab initio* molecular orbital calculations on isolated C_4Li_4 isomers are revealing. Besides *(1)*, we surveyed seven other possibilities with high symmetry at the minimal basis set level (RHF/STO-3G) employing the Gaussian 70 series of programs[8]. The structures were based on those of corresponding C_4H_4 isomers investigated previously[3b]. *(1)*, and the two most stable singlets found, *(4)* and *(5)*, were then fully optimized. The calculated geometries are shown in *(1)*, *(4)*, and *(5)*. The absolute energies are −178.63982, −178.74371, and −178.76442 Hartree (a. u.), respectively. Calculations with the split valence 4-31G basis set[8] on the STO-3G optimized structures gave absolute energies of −180.66590, −180.74831, and −180.79084 Hartree. Although *(5)* is indicated to be 26.7 kcal/mol more stable than *(4)*, the observed ^{13}C chemical shift would seem to rule out such olefinic structures[9]. Furthermore, hydrolysis of *(5)* would be expected to give cyclobutadiene which is known to dimerize rather than to dissociate[2e]. The available evidence indicates, on the other hand, that tetrahedrane should decompose to acetylene[2f].



(4), T_d



(5), D_{2h}



(6), T_d

C–C 1.592 Å		C–C 1.619, 1.376 Å	C–C 3.68 Å
C–Li 1.937 Å	calc.	C–Li 1.903, 1.792 Å	C–Li 2.31 Å

The hypothetical reactions below provide a means of evaluating the effect of Li substitution[1]. On this basis relative instability of *(2)* (195.5 kcal/mol; RHF/STO-3G)[3b] is reduced sharply by lithium substitution to 67.1 kcal/mol in *(1)*[11]. However, our calculations indicate that face-centered tetralithiotetrahedrane *(4)* is 65.2 kcal/mol *more stable* than *(1)*. The remarkably low relative instability of *(4)*, 1.9 kcal/mol, is a consequence of the stabilization of the tetrahedrane "bent bond" orbitals by lithium.

$4(CH_3)_3CX \rightarrow C_4X_4 + 6C_2H_6$

(2) X=H	+195.5 kcal/mol
(1) X=Li	+ 67.1 kcal/mol
(4) X=Li	+ 1.9 kcal/mol

Calculations at the minimal basis STO-3G level are not definitive; they tend to exaggerate the involvement of p-orbitals on lithium and to give C—Li distances which are somewhat short[12]. Nevertheless, lithium shows a general preference for bridging positions, as is shown by available X-ray[13] and calculations[4, 14], *e.g.* that for C_2Li_2 *(3)*[4].

The tetralithiotetrahedrane structure *(4)*, with lithium on the faces of a tetrahedron of carbon atoms, is reminiscent of the X-ray structure of $(CH_3Li)_4$ *(6)*[10], where methyl groups bridge the faces of a tetrahedron of lithium atoms.

The dimerization of acetylene to tetrahedrane is a photochemically allowed reaction[2c]; the nature of the photochemical process involving C_2Li_2 has yet to be delineared in detail. It is easy to visualize how the perpendicular approach of two bridged C_2Li_2 units *(3)* might yield *(4)*. Attempts to synthesize tetrahedrane derivatives by such perpendicular acetylene photodimerizations have not succeeded in the past[15], but it should be much easier to produce a strain-free product than a highly strained one. Our present evidence seems most closely in accord with a tetrahedrane structure *(4)* for C_4Li_4; we are gathering more definite information.

Experimental

Carefully cleaned Li metal (0.7 g) was dissolved in 100 ml of purified anhydrous ammonia at −50°C. Acetylene, also carefully purified, was slowly introduced just until the blue color of the solution disappeared (*ca.* 20—30 min). An argon flush eliminated any excess acetylene. The resulting 0.01 M Li_2C_2 solution in a quartz vessel was irradiated for 6 h at −45°C with a TQ150 Hanovia Hg-high pressure lamp.

The reaction course could be followed by ^{13}C-NMR spectroscopy: the C_2Li_2 singlet at $\delta=75.0$ was replaced by the C_4Li_4 singlet at $\delta=58.2$. The Raman-active C≡C vibration at 1885 cm^{-1} also disappears. The white ammonia-free powder, which can be obtained by evaporation of the solvent, is sensitive to air and moisture, decomposes slowly at room temperature, but is stable under argon at −20°C. In the solid or in solution in NH_3 or DMF, the product absorbs in the IR at 688, 612, and 448 cm^{-1}. Hydrolysis gives C_2H_2 in 98.4 % yield (gasiometrically) based on the amount of lithium used initially.

The field desorption measurements were made on a Varian MAT 311A mass spectrometer by using a combined EI/FI-ion source. The optimization of the conditions of measurement (in particular the anode current and the source potential) was achieved through visual control as well as by measurement of the total ion current in the relevant m/e region. In spite of strong fluctuations of the short-lived ion current (due to the microscopic fine structure of the emitter, the distribution of the sample on the emitter surface, and the physical properties of the sample), cyclic scanning of the $m/e=75$ and 76 peaks showed conclusively by means of the $^6Li/^7Li$ isotopic ratio that $[Li_4C_4]^+$ was present. The observed relative intensities of the $m/e=75/76$ peaks were between 0.2 and 0.4; the calculated $C_4{}^6Li^7Li_3/C_4{}^7Li_4$ ratio is 0.29. Species corresponding to $[(C_2Li_2)_n]^+$ with $n=1$ or $n\geq 3$ were never observed under any conditions[7].

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CAS Registry numbers:
(1), 65982-76-5; *(3)*, 1070-75-3; *(5)*, 65982-75-4

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[6] As shown by the Debye-Scherrer pattern. We thank Prof. Dr. *H. Burzlaff* and Dr. *E. Wilhelm* for assistance.

[7] We thank Dr. *H. Schwarz* and Dr. *G. Höhne* for determining these spectra.

[8] *W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton, J. A. Pople*, Program No. 236, Quantum Chemistry Program Exchange, University of Indiana, Bloomington, Ind. A single precision Telefunken TR 440 version of this program, written by *H.-U. Wagner*, was employed. Convergence was achieved by means of an SCF damping routine (*D. Poppinger*, unpublished).

[9] The ^{13}C-NMR chemical shifts of the lithium-bearing carbons are (THF solution, δ-values): vinyllithium, 183.4; phenyllithium, 186.4 [*J. P. C. M. van Dongen*, Dissertation, University of Utrecht, Holland, 1974]. Bicyclobutanes give $\delta(^{13}C)$ values at higher fields [*M. Christl*, Chem. Ber. *108*, 2781 (1975)].

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[11] The standard geometry RHF/STO-3G energy of $(CH_3)_3CLi$ is −162.14597 a. u. [*E. D. Jemmis*, unpublished calculation]; *J. D. Dill* (Ref. [1]) gives a value of −162.14389.

[12] *J. D. Dill, P. v. R. Schleyer, J. S. Binkley, J. A. Pople*, J. Am. Chem. Soc. *99*, 6159 (1977).

[13] See *e.g. M. Walczak, G. Stucky*, J. Am. Chem. Soc. *98*, 5531 (1976) and references cited therein.

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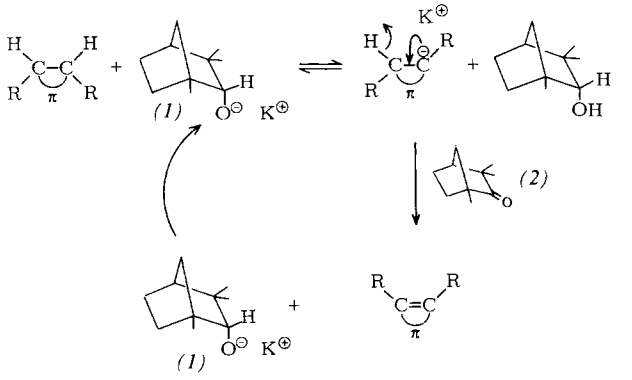
[15] *H. A. Staab, E. Wehinger, W. Thorwart*, Chem. Ber. *105*, 2290 (1972); *H. A. Staab, B. Draeger, ibid. 105*, 2320 (1972).

Deprotonation-Hydride Elimination as a Method of Dehydrogenation[1]

By *Manfred T. Reetz* and *Franz Eibach*[*]

In spite of the many dehydrogenation and aromatization agents available, conventional methods fail in some cases. If reactive arenes are formed, they undergo Diels-Alder reactions with dehydrogenation agents such as chloranil or dichlorodicyano-*p*-quinone[2, 3]. Dehydrogenations with sulfur, trityl perchlorate, iodine, or palladium are sometimes also of no preparative utility, *e.g.* in the synthesis of 9,10-dialkylanthracenes[4].

We have developed a new dehydrogenation procedure, based on deprotonation-hydride elimination. Potassium fencholate *(1)* serves as base and fenchone *(2)* as hydride acceptor[5]. Since fencholate is regenerated in the aromatization



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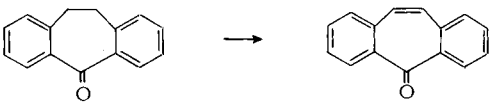
Table 1. Aromatization by fencholate-fenchone. The reaction is performed with 15—20 mol % of potassium fencholate *(1)* and an amount of fenchone equivalent to the quantity of dihydroarene in DMSO at 90°C; at 70°C in the case of benzene.

Dihydroarene	Reaction time [h]	Arene	Yield [%] [a]
1,2-Dihydronaphthalene	22	Naphthalene	95 (77)
3,4-Dihydronaphthalene	22	Naphthalene	90 (70)
9,10-Dihydroanthracene	25	Anthracene	98 (80)
9,10-Dimethyl-9,10-dihydroanthracene	30	9,10-Dimethyl-anthracene	96 (78)
9-Ethyl-10-methyl-9,10-dihydroanthracene	30	9-Ethyl-10-methylanthracene	92 (75)
5,12-Dihydrotetracene	40	Tetracene	— (85)
1,3-Cyclohexadiene	120	Benzene	68 (—)
1,4-Cyclohexadiene	120	Benzene	68 (—)
5,6-Diphenyl-2,3-dihydropyrazine	40	2,3-Diphenylpyrazine	75 (52)

[a] Yields in parentheses refer to isolated compounds; other values determined by ^1H-NMR or GC.

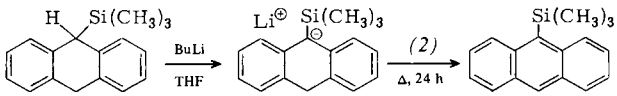
step, only catalytic quantities are required. Some smooth dehydrogenations are listed in Table 1. Remarkably good yields are obtained, even in critical cases such as 9,10-dimethyl- and 9-ethyl-10-methylanthracene[6] and tetracene[2].

In contrast to aromatization, dehydrogenation to form olefins is usually *unsuccessful* because potassium fencholate is too weak a base[7]. Certain C—H acidic compounds are exceptions; for example, the ready conversion of *(3)* into *(4)* (90 % yield).



(3) *(4)*

Although our method fails with the trimethylsilyl derivative *(5)*[7], transformation into *(6)*[8], which defies conventional methods, could nevertheless be accomplished by the deprotonation-hydride elimination technique: reaction with *n*-butyllithium followed by fenchone *(2)*[5] gives *(6)* in 80 % yield.



(5) *(6)*

Procedure

Fenchone *(2)* (0.91 g, 6 mmol) is dissolved in anhydrous DMSO (30 ml), treated with potassium hydride (*ca.* 0.04 g, 1 mmol) at room temperature, and stirred vigorously for 30 min. After addition of 9-ethyl-10-methyl-9,10-dihydroanthracene (1.11 g, 5 mmol), a clear dark red solution is obtained which is heated to 90 °C until reaction is quantitative (30 h). The reaction solution is hydrolyzed with water and extracted twice with ether (with benzene in the case of ether-insoluble arenes). The organic phase is subsequently shaken several times with water to remove residual DMSO. After drying with $MgSO_4$ the ether is removed and the residue recrystallized from ethanol.

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CAS Registry numbers:
(1), 65879-26-7; *(2)*, 1195-79-5; *(3)*, 1210-35-1; *(4)*, 2222-33-5; *(5)*, 18002-83-0; *(6)*, 56272-35-6; 1,2-dihydronaphthalene, 447-53-0; 9,10-dihydroanthracene, 613-31-0; 9,10-dimethyl-9,10-dihydroanthracene, 22566-43-4; 9-ethyl-10-methyl-9,10-dihydroanthracene, 36778-20-8; 5,12-dihydrotetra-

cene, 959-02-4; 1,3-cyclohexadiene, 592-57-4; 1,4-cyclohexadiene, 628-41-1; 5,6-diphenyl-2,3-dihydropyrazine, 1489-06-1; naphthalene, 91-20-3; anthracene, 120-12-7; 9,10-dimethylanthracene, 781-43-1; 9-ethyl-10-methylanthracene, 19713-49-6; tetracene, 92-24-0; benzene, 71-43-2; 2,3-diphenylpyrazine, 1588-89-2

[1] Hydride Eliminations, Part 6. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 5: *M. T. Reetz*, Nachr. Chem. Tech. Labor. *25*, 594 (1977).
[2] *L. M. Jackman*, Adv. Org. Chem. *2*, 329 (1960).
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[4] *R. G. Harvey, L. Nazareno, H. Cho*, J. Am. Chem. Soc. *95*, 2376 (1973).
[5] For steric reasons, fenchone does not undergo carbanion addition but only reduction by hydride transfer: *M. T. Reetz, C. Weis*, Synthesis *1977*, 135.
[6] These transformations could previously only be accomplished in preparatively useful yields by double anionization with an excess of *n*-butyllithium in tetramethylethylenediamine, followed by oxidative aromatization [4].
[7] *F. Eibach*, planned Dissertation, Universität Marburg 1978.
[8] *R. M. G. Roberts*, J. Organomet. Chem. *110*, 281 (1976).

$[(S_2)_2Mo(S_2)_2Mo(S_2)_2]^{2-}$, a Novel Complex Containing only S_2^{2-} Ligands and a Mo—Mo Bond

By *Achim Müller, Wulf-Otto Nolte*, and *Bernt Krebs*[*]

Molybdenum-sulfur compounds occur in redox-enzymes whose action involves electron transitions $Mo^{VI} \rightleftharpoons Mo^{V}$[1]; only under special conditions are lower oxidation states of molybdenum obtained in biological systems. In this connection, reactions are of interest in which Mo^{VI} is reduced to Mo^{V} only by S^{2-} or (S_n^{2-})[2] (further reduction is also not expected here).

Red-black $(NH_4)_2[(S_2)_2Mo(S_2)_2Mo(S_2)_2]\cdot 2H_2O$ *(1)* can be prepared by reduction of molybdate(VI) (or thiomolybdates) with polysulfide ions in aqueous solution and could be characterized by elemental analysis, DTA, TG, and magnetic measurements, its ESCA and IR spectrum along with a single crystal structure analysis. *(1)* is diamagnetic and exhibits absorption bands due to the anion at 530 [m; ν(S—S)], 340 and 360 cm^{-1} [w; ν(MoS)]. The positions of the ν(MoS) bands show the absence of the terminal Mo—S bonds with π-bonding contributions[3a] which have so far only been found in the case of Mo^{VI}[3b]. The compound is stable and is moderately soluble in water (decomposing after a short time[4]).

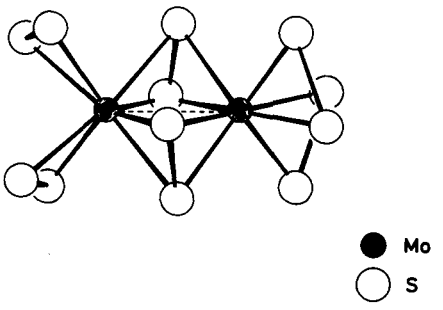


Fig. 1. Structure of the complex anion $[(S_2)_2Mo(S_2)_2Mo(S_2)_2]^{2-}$ in crystals of *(1)*.

(1) crystallizes in the rhombic space group Pnna-D_{2h}^6 with $a=21.613$, $b=13.127$, $c=12.576$ Å and $Z=12$. According to the X-ray structure analysis the asymmetric unit of the unit cell contains two crystallographically independent dimeric anions $[(S_2)_2Mo(S_2)_2Mo(S_2)_2]^{2-}$ (cf. Fig. 1). Both the Mo^{V} centers are dodecahedrally (distorted) surrounded by eight sulfur atoms (four disulfide groups). The "side-on" bonding of all the S_2^{2-} ligands to the central atom is slightly asymmetric with two slightly different Mo—S distances [2.382(4)...2.454(4) and 2.463(4)...2.507(4) Å]. The S—S bond lengths of 2.035(6)...2.063(6) Å correspond to a normal single bond. The Mo—Mo distances in the ions amount to 2.826(2) and 2.828(2) Å, which together with the magnetic properties suggest a central Mo—Mo bond[5]. Thus, molybdenum has the unusual coordination number 9. A similar kind of bonding of disulfide groups to a Mo^{VI} center (with a coordination number of 7) was observed in $[MoO(S_2)_2(COS—COO)]^{2-}$[6].

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Experimental

Into an aqueous ammonia solution (dilute, 30 ml) of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (2 g) is passed H_2S until saturation (any precipitated $(NH_4)_2MoS_4$ can be redissolved by heating). This red solution is added to a saturated ammonium polysulfide solution. A precipitate slowly separates from this reaction mixture kept in a closed container (long needles growing out of the crystal mass)[7]. The substance is washed several times with ethanol, with ether, and with carbon disulfide, and dried over P_4O_{10} at normal pressure (yield *ca.* 80%; needles 5–10%)[8].

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CAS Registry numbers:
(1), 65878-95-7; $(NH_4)_2MoS_4$, 15060-55-6; $(NH_4)_6Mo_7O_{24}$, 12027-67-7; H_2S, 7783-06-4; ammonium polysulfide, 9080-17-5

[1] a) *A. E. Dennard, R. J. P. Williams*, Transition Met. Chem. *2*, 115 (1966); *R. C. Bray, L. S. Meriwether*, Nature *212*, 467 (1966); b) *M. N. Hughes*: The Inorganic Chemistry of Biological Processes. Wiley, New York 1974.
[2] Since CN^- is probably also bound to the metal (as inhibitor) [1b] in Mo-enzymes, analogous reaction in the presence of CN^- also seems to be interesting; for the isolation of $K_6[(CN)_6MoSMo(CN)_6]\cdot 4H_2O$ cf. *A. Müller, P. Christophliemk*, Angew. Chem. *81*, 752 (1969); Angew. Chem. Int. Ed. Engl. *8*, 753 (1969).
[3] a) *K. H. Schmidt, A. Müller*, Coord. Chem. Rev. *14*, 115 (1974); b) *E. Diemann, A. Müller, ibid. 10*, 79 (1973).
[4] Molybdenum compounds with higher sulfur content were already mentioned in the literature of the last century, for which valence states of molybdenum >6 have been assumed. Some experimental results are not reproducible (review: [3b]).
[5] See *D. L. Stevenson, L. F. Dahl*, J. Am. Chem. Soc. *89*, 3721 (1967).
[6] *K. Mennemann, R. Mattes*, Angew. Chem. *89*, 269 (1977); Angew. Chem. Int. Ed. Engl. *16*, 260 (1977).
[7] A large amount of long needles is obtained if the reaction vessel is left indisturbed for *ca.* 12d. The crystal mass is chemically identical with the needles but purification according to the procedure given is more difficult.
[8] *(1)* has meanwhile been obtained by various methods (*e.g.* from Mo^{V}-containing solutions by reaction with polysulfide). This constitutes proof of its pronounced formation tendency (*A. Müller et al.*, to be published).

A One-Step Synthesis of Vinylsilanes and Vinylenebissilanes

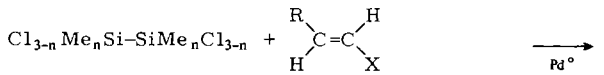
By *Hideyuki Matsumoto, Shigeru Nagashima, Takayuki Kato*, and *Yoichiro Nagai*[*]

Recently, vinylsilanes have received much interest as useful reagents in organic synthesis and polymer chemistry. Hydrosi-

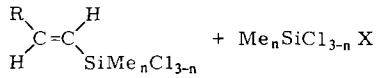
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lylation of alkynes is one of the most straightforward routes to these compounds, but the product is often accompanied by 1,2-disilylethanes[1]. Condensation between a hydrosilane and a haloethene requires drastic conditions[2], while treatment of vinylic Grignard reagents with chlorosilanes requires solvents such as ether, THF, or HMPA to promote the reaction[3].

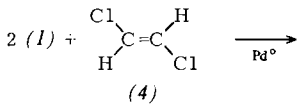
We have found that vinylsilanes and vinylenebissilanes can be conveniently prepared by the reaction between a disilane and a haloethene in the presence of a homogeneous palladium(0) catalyst. Vinylsilanes *(3)* (Table 1) were prepared by heating a mixture of a chloro(methyl)disilane *(1)*[4], a haloethene *(2)*, and tetrakis(triphenylphosphane)palladium(0)[5] as catalyst in a sealed reaction vessel or an open apparatus. Thus Pd^0-catalyzed reaction of (*E*)-1,2-dichloroethene *(4)* with two equivalents of *(1)* gives vinylenebissilane *(5)* (Table 1).



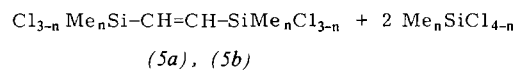
(1a), n = 1 *(2a)*, R = H, X = Cl
(1b), n = 2 *(2b)*, R = Ph, X = Br



(3a) - (3d)



(4)



(5a), *(5b)*

Table 1. Vinylsilanes *(3)* and vinylenebissilanes *(5)* prepared.

Cpd.	R	*n*	X	Yield [%] [a]	*E*:*Z*
(3a)	H	1	Cl	45	
(3b)	H	2	Cl	56	
(3c)	Ph	1	Br	85 (76)	
(3d)	Ph	2	Br	83 (72)	
(5a)		1		86	9:1
(5b)		2		80 (50)	9:1

[a] Yields determined by GLC; isolated yields given in parentheses.

The hitherto unknown vinylenebissilane *(5b)* is expected to be a precursor of novel siloxane polymers.

Experimental

Synthesis of *(3c)*: A mixture of *(1a)* (8.39 g, 42 mmol), (*E*)-*(2b)* (7.35 g, 40 mmol), and Pd^0 catalyst (0.24 g, 0.2 mmol) is refluxed under nitrogen for 1 h with stirring. The mixture is diluted with *n*-pentane (40 ml) and the precipitated catalyst filtered off. Evaporation of low boiling materials and subsequent distillation gives (*E*)-*(3c)* (6 g) in 99 % purity. The product was identified by its ^{1}H-NMR, IR, and mass spectrum.

Synthesis of *(5b)*:*(4)* (32 g, 340 mmol), *(1b)* (131 g, 700 mmol), and the palladium(0) catalyst (1.16 g, 1.0 mmol) were introduced into a stainless steel vessel. The vessel was flushed with nitrogen, sealed and heated at 180 °C for 15 h. Work-up gave 36 g of (*E*)- and (*Z*)-*(5b)* (9:1) in 98 % purity as a colorless liquid. (*E*)-*(5b)*: ^{1}H-NMR (CCl_4) $\delta = 0.56$ (s, 12H), 6.77 (s, 2H); IR (neat) 2950, 1405, 1255, 1000, 840, 815, 790, 650 cm^{-1}; mass spectrum (70 eV): $m/e = 212$ (M^+).

(*Z*)-*(5b)*: ^{1}H-NMR (CCl_4) $\delta = 0.56$ (s, 12H), 6.82 (s, 2H); IR (neat) 2950, 1405, 1255, 925, 840, 810, 800, 695, 650 cm^{-1}; mass spectrum (70 eV): $m/e = 212$ (M^+).

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CAS Registry numbers:
(1a), 4518-98-3; *(1b)*, 4342-61-4; *(2a)*, 75-01-4; *(2b)*, 588-72-7; *(3a)*, 124-70-9; *(3b)*, 1719-58-0; *(3c)*, 17902-47-5; *(3d)*, 61518-55-6; *(4)*, 156-60-5; *(E)-(5a)*, 65899-10-7; *(Z)-(5a)*, 65899-09-4; *(E)-(5b)*, 65899-08-3; *(Z)-(5b)*, 65899-07-2

[1] *C. Earbon, R. W. Bott* in *A. G. MacDiarmid:* Organometallic Compounds of the Group IV Elements. Vol. 1. Marcel Dekker, New York 1968, p. 269.
[2] *A. D. Petrov, B. F. Mironov, V. A. Ponomarenko, E. A. Chernyshev:* Synthesis of Organosilicon Monomers. Consultants Bureau, New York 1964, p. 128.
[3] *S. D. Resenberg, J. J. Walburn, T. D. Stankovich, A. E. Balint, H. E. Ramsden*, J. Org. Chem. *22*, 1200 (1957); *D. Seyferth, L. G. Vaughan, R. Suzuki*, J. Organometal. Chem. *1*, 437 (1964); *J. Donogues, J.-P. Pillot, N. Duffaut, R. Calas*, C. R. Acad. Sci. *C 278*, 467 (1974).
[4] *H. Watanabe, N. Kobayashi, Y. Koike, S. Nagashima, H. Matsumoto, Y. Nagai*, J. Organomet. Chem. *128*, 173 (1977); *H. Matsumoto, T. Motegi, M. Hasegawa, Y. Nagai, ibid. 142*, 149 (1977).
[5] *H. Matsumoto, S. Nagashima, K. Yoshihiro, Y. Nagai*, J. Organometal. Chem. *85*, C 1 (1975); *D. Azarian, S. S. Dua, C. Earbon, D. R. M. Waltone, ibid. 117*, C 55 (1976); *H. Matsumoto, K. Yoshihiro, S. Nagashima, Y. Nagai, ibid. 128*, 409 (1977); *H. Matsumoto, T. Yako, S. Nagashima, T. Motegi, Y. Nagai, ibid.*, in press.

Molecular Structure of $[Mn(CO)_4NSOF_2]_2$— A Dinuclear Transition Metal Complex Containing Difluorooxosulfimidato Bridges[**]

By *Bruno Buss, Dieter Altena, Rüdiger Mews*, and *Oskar Glemser*[*]

Preliminary studies on the dimeric species $[M(CO)_4NSOF_2]_2$ with M = Mn, Re ans $NSOF_2$ groups as bridging ligands failed to establish whether the metal atoms are linked *via* nitrogen-sulfur-oxygen bridges or only by the nitrogen atoms of the $F_2S(O)$=N ligands[1]. In the last-mentioned case, these complexes should possess a structure analogous to $[Mn(CO)_4Br]_2$[2]. The donor strength of the ligand and the effect of coordination on the NS bond also remain to be established.

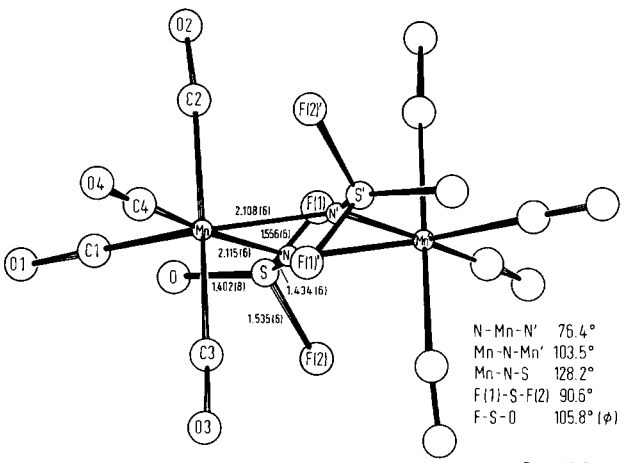


Fig. 1. Molecular structure of the dinuclear manganese complex $[Mn(CO)_4NSOF_2]_2$ with principal bond lengths [Å] and angles [°].

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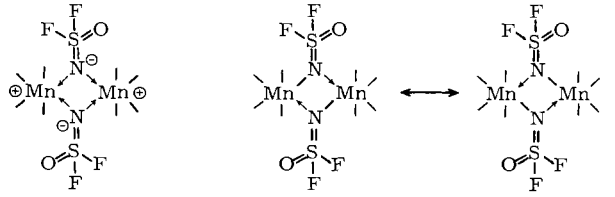
[**] This work was supported by the Deutsche Forschungsgemeinschaft.

An X-ray structure analysis[3] of the manganese complex has now shown the isolated molecule to contain two octahedral units joined by a shared edge (cf. Fig. 1).

The central moiety containing the Mn, N, and S atoms is almost planar, while the Mn_2N_2 four-membered ring is exactly planar, showing that the nitrogen atoms no longer possess a stereochemically effective lone pair. All the Mn—N distances are equal within the limits of error and somewhat longer than would correspond to a single bond (based on the covalent radius of 1.39 Å for Mn^0[4]). Both the Mn···Mn' distance of 3.318(2) Å and the angle in the central portion of the molecule show that no direct metal-metal bond is present; the small N—Mn—N' angle (76°) even suggests a repulsive interaction between the two Mn atoms.

The $NSOF_2$ group serving as bridge has a strongly distorted tetrahedral symmetry. The S—O and S—F bond lengths closely resemble those in other compounds R—$NSOF_2$[5]. The very short N—S bond of 1.434(6) Å corresponds to a bond order of *ca.* 2.5[6] and indicates strong d_π-p_π bonds between sulfur and nitrogen; it is *ca.* 0.05 Å shorter than in $ClNSOF_2$[5a] and—within the limits of error—of the same length as in $(CO)_5ReNSOF_2$[5b]. The $NSOF_2$ groups of $[Mn(CO)_4NSOF_2]_2$ can be formally regarded as four-electron donors [cf. *(1a)*], and in the compounds R—$NSOF_2$ with R = Cl and $Re(CO)_5$ as two-electron donors. However, the surprisingly large Re—N—S angle of 140° in $(CO)_5ReNSOF_2$ suggests a bonding contribution from the nitrogen lone pair; in $ClNSOF_2$, on the other hand, the lone pair is fully effective (Cl—N—S: 114°)[5a].

There are two possible ways of describing the bonding: the manganese atoms have the oxidation number +1 in *(1a)* and 0 in *(1b)*, the $NSOF_2$ group being considered as a four- or three-electron donor. No decision in favor of either of these two alternatives is possible on the basis of available experimental evidence.



(1a) *(1b)*

The bonds of the CO ligands correspond to those in other carbonyl complexes[7]; nevertheless, the *trans* effect (Mn—C_{eq} = 1.807 Å, Mn—C_{ax} = 1.899 Å) is relatively pronounced.

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revised: February 6, 1978 [Z 929 IE]
German version: Angew. Chem. *90*, 287 (1978)

CAS Registry numbers:
$[Mn(CO)_4NSOF_2]_2$, 65915-49-3

[1] *R. Mews, O. Glemser*, J. Chem. Soc. Chem. Commun. *1973*, 823.
[2] *L. F. Dahl, C. H. Wei*, Acta Crystallogr. *16*, 611 (1963).
[3] 1050 independent diffractometer data, solution by conventional methods, refined with anisotropic temperature factors to $R = 7.1\,\%$; space group $P2_1/n$ (standard formulation $P2_1/c$-C_{2h}^5, No. 14), $Z = 2$; lattice constants (20°C): $a = 1002.4(5)$, $b = 1175.1(5)$, $c = 736.8(4)$ pm, $\beta = 100.96(4)°$, $d_{calc.} = 2.08$, $d_{exp.} = 2.10\,g\,cm^{-3}$.
[4] *F. A. Cotton, D. C. Richardson*, Inorg. Chem. *5*, 1851 (1966).
[5] a) *H. Oberhammer, O. Glemser, H. Klüver, Z.* Naturforsch. *A29*, 901 (1974); b) *B. Buss, D. Altena*, to be published.
[6] *O. Glemser, A. Müller, D. Böhler, B. Krebs*, Z. Anorg. Allg. Chem. *357*, 184 (1968).
[7] Cf., *e.g., R. Bau, S. W. Kirtley, T. N. Sorrell, S. Winarko*, J. Am. Chem. Soc. *96*, 988 (1974); *S. J. La Placa, W. C. Hamilton, J. A. Ibers, A. Davison*, Inorg. Chem. *8*, 1928 (1969); references cited therein.

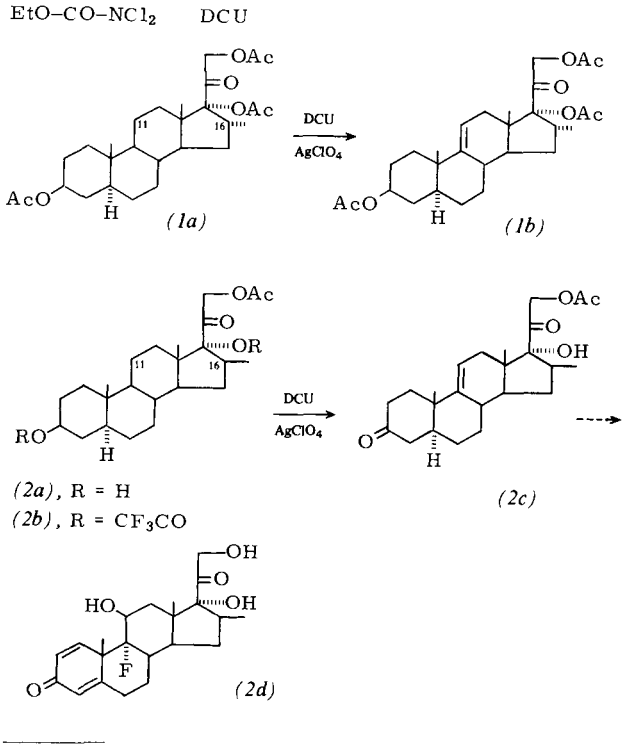
N,N-Dichlorourethane—A Selective Chlorination Reagent; Synthesis of Corticoids

By *Yehuda Mazur* and *Zvi Cohen*[*]

Continuing our studies on the selective functionalization of steroid molecules[1], we searched for a simple method to introduce a functional group at C_{11} in deoxycorticoids, to replace the microbiological method commonly used for this purpose.

We have now found that saturated steroids can be selectively chlorinated with *N,N*-dichlorourethane (DCU).

DCU is a stable, distillable, but highly reactive pseudohalogen which is easily prepared by reacting urethane with chlorine[2]. This compound was found by *Chabrier*[3] to add to olefins, giving the unstable *N*-chloro-*N*-(β-chloroalkyl)carbamates, which can be readily reduced to the *N*-(β-chloroalkyl)-carbamates. We observed that cyclohexane on exposure to light in the presence of DCU is converted into chlorocyclohexane and urethane and that benzene solutions of adamantane and DCU on irradiation with a sunlamp gave 1-chloroadamantane in high yields. Reaction of DCU with steroids resulted mainly in chlorination at C-9:androstane-3β,17β-diyl diacetate was converted into a mixture of tertiary chlorides, which after dehydrochlorination with $AgClO_4$ gave the corresponding 9(11)- and 14-androstene derivatives in 40 and 9 % yield, respectively[4]. In the case of steroids with dihydroxyacetone side chains, DCU proved to be even more selective. We have chosen *(1a)* and *(2a)* as starting compounds; these compounds are intermediates in the preparation of the medically useful 16α- and 16β-methylcorticoids[5].



(1a) *(1b)*

(2a), R = H
(2b), R = CF_3CO

(2c) *(2d)*

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The diacetate *(1a)*[5] was irradiated in the presence of DCU in benzene and then dehydrochlorinated with $AgClO_4$; the only product was the corresponding 9(11)-pregnene derivative *(1b)* (yield 41 %). For the synthesis of the 9α-fluoro-16β-methylcorticoid *(2d)*, the acetate *(2a)*[5] was converted into the bis(trifluoroacetate) *(2b)*[4], which was then treated with DCU, and finally with $AgClO_4$. Subsequent hydrolysis of the trifluoroacetyl groups with NaN_3 in methanol[6] and oxidation with pyridinium chlorochromate afforded the known ketone *(2c)*[7a] [55 % yield based on *(2b)*], which is easily converted into the glucocorticoid *(2d)*[7b].

There is a close analogy between the halogenation reactions with DCU and those with iodobenzenedichloride[8]: both reactions proceed by a free radical chain mechanism involving photochemically generated chlorine atoms. These chlorine atoms serve as hydrogen abstracting radicals, as seen by comparing the reactivity of the tertiary and the primary hydrogens in 2,3-dimethylbutane. In chlorinations with DCU this ratio was found to be 89:1 in CS_2, 50:1 in benzene and 9:1 in the absence of a solvent while the respective ratios for reactions with chlorine at comparable temperatures and concentrations as found by *Russell*[9] were 109:1, 49:1 and 4:1.

N-Monochlorourethane, which occurs as intermediate, can also serve as a chlorination reagent, however it is much less effective than DCU.

Procedure

Synthesis of *(1b)*. A solution of *(1a)* (1 g, 2.04 mmol) and DCU (0.65 g, 4.12 mmol) in dry benzene (150 ml) flushed with N_2 was irradiated with a 160W-sunlamp for 10 h in an atmosphere of N_2. The reaction mixture was washed with $NaHSO_3$, dried, and evaporated to dryness. The residue was dissolved in acetone (150 ml) and treated with an aqueous solution of $AgClO_4$ (6 g in 60 ml). The precipitate formed was filtered off, the solvent evaporated and the residue extracted with ether and washed with water. Subsequent column chromatography (dry SiO_2, CH_2Cl_2) afforded *(1b)* (0.41 g, 41 %), m.p. 138—139 °C, $[\alpha]_D = -15°$, ^{1}H-NMR ($CDCl_3$): $\delta = 0.95$ and 5.32 (H at C-19 and C-9).

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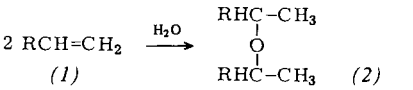
CAS Registry numbers:
(1a), 65899-44-7; *(1b)*, 65899-43-6; *(2a)*, 21670-48-4; *(2b)*, 65899-45-8; *(2c)*, 13852-68-1; *(2d)*, 378-44-9; DCU, 13698-16-3

[1] *Y. Mazur*, Pure Appl. Chem. *41*, 145 (1975); *Z. Cohen, E. Keinan, Y. Mazur, A. Ulman*, J. Org. Chem. *41*, 2651 (1976); and references cited therein.
[2] *T. A. Foglia, D. Swern*, J. Org. Chem. *31*, 3625 (1966); *33*, 766 (1967).
[3] *P. Chabrier*, Fr. Pat. 56285 (1952).
[4] All the new compounds were characterized by ^{1}H-NMR-, ^{13}C-NMR- and mass spectra.
[5] We thank Dr. *H. Herzog* (Schering Co., Bloomfield, N.J.) for supplying samples of *(1a)* and *(2a)*. Cf. *E. P. Oliveto, R. Rauser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, M. M. Pechet*, J. Am. Chem. Soc. *80*, 4431 (1958).
[6] *L. Weber, E. L. Shapiro, L. E. Finckenor, H. L. Herzog*, US-Pat. 3383394 (1968).
[7] a) *J. A. Attenburrow, J. E. Connet, W. Graham, J. F. Oughton, A. C. Richie, P. Wilkinson*, J. Chem. Soc. *1961*, 4547; b) *T. R. Carrington, S. Eardley, J. Elks, S. F. H. Green, G. I. Gregory, A. G. Long, J. C. P. Sly, ibid. 1961*, 4560.
[8] *R. Breslow, R. J. Corcoran, J. A. Dale, S. Liu, P. Kalicky*, J. Am. Chem. Soc. *96*, 1973 (1974); *R. Breslow, R. J. Corcoran, B. B. Snider, ibid. 96*, 6791 (1974); *R. Breslow, B. B. Snider, R. J. Corcoran, ibid. 96*, 6792 (1974).
[9] *G. A. Russell*, J. Am. Chem. Soc. *80*, 4987 (1958).

Organic Syntheses Using Sheet Silicate Intercalates: Low-temperature Conversion of Olefins to Secondary Ethers[**]

By *John M. Adams, James A. Ballantine, Samuel H. Graham, Richard J. Laub, J. Howard Purnell, Paul I. Reid, Wafa Y. M. Shaman*, and *John M. Thomas*[*]

We have discovered that a range of cation-exchanged montmorillonites will smoothly convert 1-alkenes *(1)* to the corresponding secondary ethers *(2)* when hexane solutions of the olefin are refluxed in presence of the solid montmorillonite for 5—10 h.



(a), R = *n*-C_4H_9; *(b)*, R = *n*-C_5H_{11}; *(c)*, R = *n*-C_6H_{13}

GLC, mass spectrometry and the ^{1}H-NMR spectrum established the identity of the product. It cannot be efficiently produced by any other known preparative method. Chromatographic separation of the diastereoisomers was possible.

A range of definitive experiments[1] demonstrated that the source of the ether oxygen was the interlamellar water (hydration sphere of inorganic cation) and that reaction takes place in the interlamellar region, there being an optimal water content for a given cation of the original sheet silicate (see Fig. 1).

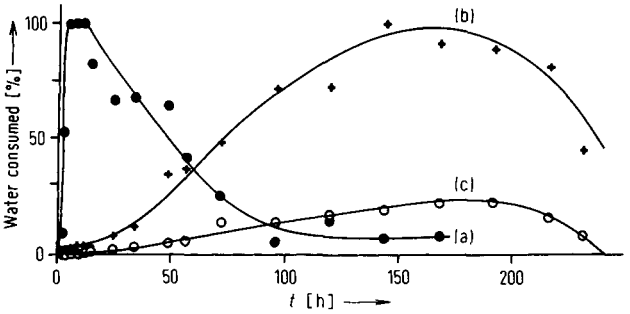


Fig. 1. Yield of ether (expressed as percentage consumption of interlamellar water) as a function of time for clays with (a) one layer (b) two layers and (c) three layers of water between the aluminosilicate sheets. 0.5 g clay was used in each case with 5 g hex-1-ene.

The montmorillonite principally used in the work had a cation-exchange capacity of 66 mequiv/100 g of air-dry aluminosilicate, but tests on montmorillonites from a number of different sources showed that all were effective for the conversion *(1)*→*(2)*. In the preliminary experiments described here, a considerable excess of alkene over aluminosilicate was employed. Yields of up to 65 %, based on consumed

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[**] Work supported by the Science Research Council.

1-alkene, and of up to 100 %, based on available interlamellar water, could be obtained.

Numerous ions facilitate the conversion, the most efficient being Cu^{2+}, Fe^{2+}, Fe^{3+}, Cr^{3+}, and Al^{3+}. For Cu^{2+} the optimal metal : water ratio is *ca.* 1 : 12. Even though the conditions in the interlamellar regions are crucial, the role of the silicate sheet itself is not unimportant since a Cu^{2+}-exchanged sheet phosphate, $Cu(UO_2PO_4)_2 \cdot 6H_2O$, the Cu^{2+} analog[2] of the mineral autinite[3], $Ca(UO_2PO_4)_2 \cdot nH_2O$, does not effect conversion of the alkene.

Experimental

Cation exchange of the montmorillonite is effected by treatment with aqueous solutions (0.3 M —1.0 M) of appropriate cations for 48 h. The clay is then washed free of excess cation with de-ionized water, surplus water is decanted off and the clay dried at 80 °C, then ground to pass through an ASTM 150 mesh sieve.—A 250 ml round-bottom flask, fitted with reflux condenser and mechanical stirrer is charged with a solution of 1-alkene *(1)* (6.4 g) in *n*-hexane (12 ml) and with cation-exchanged montmorillonite (1 g), and the mixture is stirred and refluxed for up to 24 h. The cooled solution is filtered free from clay and analyzed by gas-liquid chromatography (3 meter column packed with 3 % PEG 20M on Chromosorb G; known quantity of nonan-5-one as standard). The ether *(2)* can be isolated by preparative gas-liquid chromatography.

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CAS Registry numbers:
(1a), 592-41-6; *(1b)*, 592-76-7; *(1c)*, 111-66-0; *(2a)*, 57821-86-0; *(2b)*, 31039-13-1; *(2c)*, 20012-50-4; montmorillonites, 1318-93-0

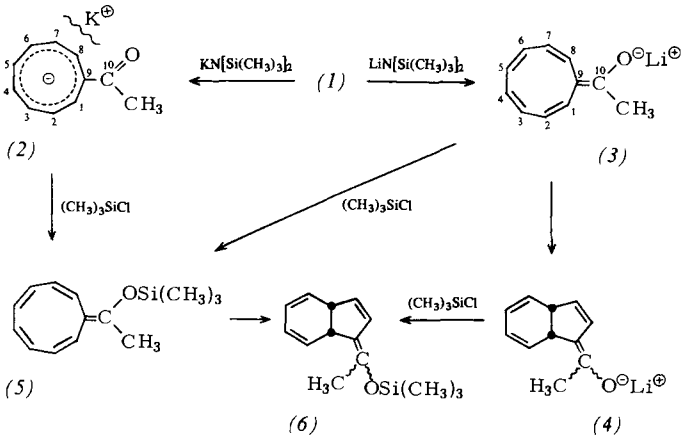
[1] *J. M. Thomas et al.*, unpublished.
[2] We thank Dr. *A. T. Howe*, University of Leeds for providing this material.
[3] *J. Beintema*, Rec. Trav. Chim. Pays Bas *57*, 155 (1938).

Alkali Metal Salts of RC(O)-Substituted Cyclononatetraenyl Anions: Aromatic [9]Annulene Anion or Olefinic Nonafulvene Structure as Function of Gegenion and Solvent[**]

By *Gernot Boche* and *Frank Heidenhain*[*]

Alkali metal salts of acceptor-substituted cyclononatetraenyl anions can exhibit the character of an aromatic or of an olefinic 10 π electron system—*e.g. (2)* or *(3)*[1]. We report here on such compounds containing RC(O)-substituents. Structurally they are of interest regarding the constitution of metal enolates[2] and of RC(O)-substituted azonines[3]. Furthermore, these compounds are intermediates for the synthesis of nonafulvenes[1b].

Reaction of 9-acetyl-*cis,cis,cis,cis*-cyclonona-1,3,5,7-tetraene *(1)*[4] with *potassium* bis(trimethylsilyl)amide in tetrahydrofuran at −78 °C led to the anion *(2)*, whose aromatic character is confirmed by spectroscopic and chemical data. ^{1}H-NMR (THF, δ rel. TMS int.): 6.83 (m, H^2 to H^7), 7.75 (d, H^1 and H^8, $J = 12.5$ Hz); ^{13}C-NMR *(vide supra)* 107.2, 111.7, 112.3, 114.8, 117.0 (C^9), 205.1 (C^{10}); the signals of *(2)* thus appear in the range of the aromatic all-*cis*-[9]annulene anion[1a] (^{1}H-NMR: $\delta = 7.02$; ^{13}C-NMR: $\delta = 109.5$). The high thermal stability of *(2)*—no isomerization takes place even on heating at 60 °C for four days—is consistent with the NMR findings.



A completely different result was obtained on reaction of *(1)* with *lithium* bis(trimethylsilyl)amide. In this case all data were consistent with the product having the fulvene structure *(3)*. ^{1}H-NMR *(vide supra)*: 5.02 (dd, H^4 and H^5, $J = 12.5$ and 3.5 Hz), 5.37—5.88 (m, H^2, H^3, H^6, H^7), 6.33 (d, H^1 and H^8, $J = 12.5$ Hz); ^{13}C-NMR *(vide supra)*: 116.0 (C^9), 124.3—130.6 (C^1 to C^8), 146.8 (C^{10}). The isomerization to the dihydroindene derivative *(4)*, observable with a halflife of 14 min in tetrahydrofuran at 50 °C, is in accord with the NMR findings.

Reaction of *(2)* or *(3)* with trimethylchlorosilane in tetrahydrofuran at −78 °C afforded the silyl enol ether *(5)* in 95 % yield. ^{1}H-NMR ($CDCl_3$, −25 °C, δ rel. TMS int.): 0.23 (s, $Si(CH_3)_3$, 1.95 (s, CH_3), 5.47 (dd, H^4 and H^5, $J = 12.5$ and 3.5 Hz), 5.66—6.07 (m, H^2, H^3, H^6, H^7), 6.27 (d, H^1 and H^8, $J = 12.5$ Hz); ^{13}C-NMR *(vide supra)*: 116.0 (C^9), 122.5—129.0 (C^1 to C^8), 150.2 (C^{10}). With these spectroscopic data and the facile isomerization ($\tau_{1/2}$ in $CDCl_3$ at 50 °C: 3 min) to *(6)*[5], which is also accessible from *(4)* and trimethylchlorosilane, the silyl enol ether *(5)* also affords supporting evidence for the fulvene structure of the lithium compound *(3)*.

The tendency of the lithium cation to form strong contact ion pairs with the enolate oxygen[2, 6] is dramatically illustrated by the breakdown of the aromatic character in *(3)*. Almost as in the silyl enol ether *(5)*, the nine-membered ring barely possesses any negative charge. The corresponding sodium compound in tetrahydrofuran at room temperature also behaves similarly to *(3)*. In the case of the potassium compound *(2)*—as opposed to "normal" potassium enolates[6]—however, drastic changes take place. The steric demands of the nine-membered ring and the tendency toward charge delocalization lead to cleavage of the weak contact ion pair and formation of a solvent-separated ion pair. Its presence in *(2)* is suggested by the fact that THF solutions of *(3)* containing hexamethylphosphoric triamide or dimethyl sulfoxide show the same ^{1}H-NMR spectrum as *(2)*. Aromaticity thus becomes an ion-pair effect[7]!

Noteworthy is the different extent of perturbation caused by the RC(O) group on the aromatic 10 π electron perimeters of the [9]annulene anion and the azonine: whereas there is hardly any noticeable effect in the case of the solvent-separated anion *(2)*, RC(O)-substituted azonines are to be characterized as olefins[3].

As the high yield (95 %) of silyl enol ether *(5)* shows, RC(O)-substituted cyclononatetraenyl anions provide a convenient entry to the nonafulvenes[1b]. Thus, reaction of *(2)*

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with acetyl chloride affords 10-acetoxy-10-methylnonafulvene in 80% yield[8].

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CAS Registry numbers:
(1), 65969-45-1; *(2)*, 65969-46-2; *(3)*, 65969-47-3; *(E)-(4)*, 65969-48-4; *(Z)-(4)*, 65969-49-5; *(5)*, 65969-50-8; *(E)-(6)*, 65969-51-9; *(Z)-(6)*, 65969-52-0; $KN[Si(CH_3)_3]_2$, 40949-94-8; $LiN[Si(CH_3)_3]_2$, 4039-32-1; $(CH_3)_3SiCl$, 75-77-4; 10-acetoxy-10-methylnonafulvene, 65969-53-1

[1] Cf. a) *G. Boche, D. Martens, W. Danzer*, Angew. Chem. *81*, 1003 (1969); Angew. Chem. Int. Ed. Engl. *8*, 984 (1969); *G. Boche, H. Weber, D. Martens, A. Bieberbach*, Chem. Ber., in press; references cited therein; b) *K. Hafner, H. Tappe*, Angew. Chem. *81*, 564 (1969); Angew. Chem. Int. Ed. Engl. *8*, 593 (1969); *M. Neuenschwander, A. Frey*, Chimia *29*, 212 (1975); *31*, 333 (1977); references cited therein.

[2] Review: *L. M. Jackman, B. C. Lange*, Tetrahedron *33*, 2737 (1977); *R. Gompper, H. U. Wagner*, Angew. Chem. *88*, 389 (1976); Angew. Chem. Int. Ed. Engl. *15*, 321 (1976).

[3] Review: *A. G. Anastassiou*, Acc. Chem. Res. *5*, 281 (1972); see also *A. G. Anastassiou, E. Reichmanis, S. J. Girgenti*, J. Am. Chem. Soc. *99*, 7393 (1977).

[4] *(1)* was prepared in 95% yield by reaction of sodium cyclononatetraenide with acetyl chloride in tetrahydrofuran at −20°C.

[5] The mixture of isomers regarding the exocyclic double bond has not as yet been resolved.

[6] *H. O. House, A. V. Prabhu, W. V. Phillips*, J. Org. Chem. *41*, 1209 (1976); *L. M. Jackman, R. C. Haddon*, J. Am. Chem. Soc. *95*, 3687 (1973); and literature cited therein.

[7] The properties of the benzoyl compounds corresponding to the acetyl compounds *(2)* and *(3)* are wholly analogous.

[8] In addition, a mixture of *C*-acylation products is obtained in 12% yield.

Reduction of 1,3-Diphenylallyl Anions *via* Dianion Radicals to Trianions with Lithium, Sodium, Potassium, and Cesium as Gegenions[**]

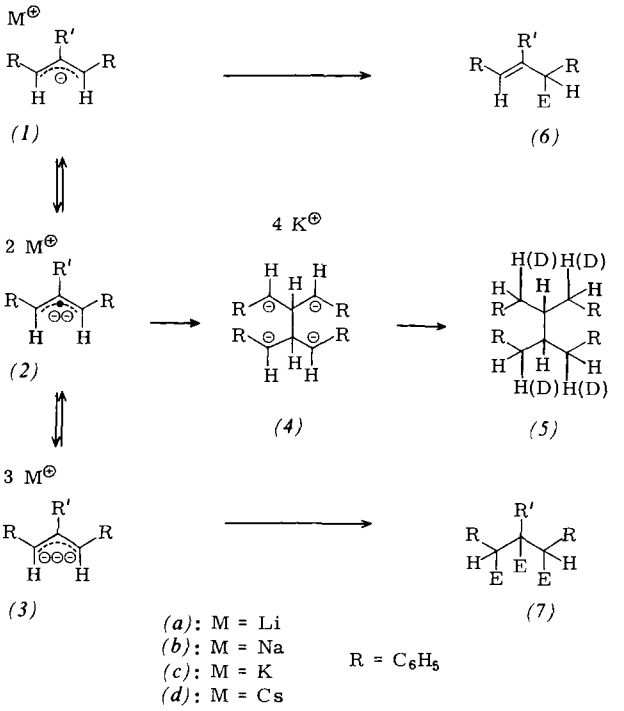
By *Gernot Boche* and *Klaus Buckl*[*]

Electron transfer reactions are of special interest both from a preparative as well as from a mechanistic point of view. We recently reported the oxidation of allyl anions to allyl radicals[1]; we now wish to describe their reduction to allyl dianion radicals and allyl trianions.

Reaction of 1,3-diphenylallyllithium[2] *(1a)*, R′=H, with potassium in tetrahydrofuran (THF) led, after 3—10 hours' stirring at room temperature and workup with D_2O, to the fourfold deuterated hydrocarbon *(5)* in 15±5% yield[3], whose constitution was confirmed by an independent synthesis[4]. Since *(5)* was formed from the tetraanion *(4)*, which in turn was produced by dimerization of the dianion radical *(2c)*, R′=H, this reaction sequence observable only in the case of *(1a)*, R′=H, demonstrates primary electron transfer. The nondimerized dianion radical was further reduced to the trianion *(3c)*, R′=H, whose structure could be proven by protonation with H_2O or deuteration with D_2O to *(7)*, R′=H, E=H[5a] or D[5b].

Triphenylallyllithium[6] *(1a)*, $R'=C_6H_5$, can be reduced with Li-, Na-, and K-naphthalene[7] and with lithium, sodium, potassium, or cesium. In no case was dimerization of the dianion radicals *(2a—d)*, $R'=C_6H_5$, observed—presumably for steric reasons—but exclusive formation of the reddish brown *(3a—c)*, $R'=C_6H_5$, or black *(3d)*, $R'=C_6H_5$, allyl trianions.

Structural proof was again provided by reaction with electrophiles. Thus, protonation with H_2O gave the hydrocarbon



(7), E=H, $R'=C_6H_5$[5a], while reaction with D_2O afforded the corresponding trideuterio compound *(7)*, E=D, $R'=C_6H_5$ (95% yield in both cases). Reaction with dimethyl sulfate gave the trimethyl compound *(7)*, $E=CH_3$, $R'=C_6H_5$, in 84% yield.

However, not all electrophiles react in this way: Diethyl sulfate affords the olefin *(6)*, $E=C_2H_5$, $R'=C_6H_5$, in 42% yield, while reaction with methyl iodide and with trimethylchlorosilane leads to the olefins *(6)*, $E=CH_3$ or $Si(CH_3)_3$[6], $R'=C_6H_5$, in 91% and 81% yield, respectively. The allyl trianion *(3)*, $R'=C_6H_5$, is therefore a nucleophile, which is particularly prone to undergo electron-transfer reactions.

This property was also manifested by the reaction with electron acceptors. Thus, iodine was converted into iodide, and nitrobenzene into the nitrobenzene dianion[8], the allyl trianion *(3)*, $R'=C_6H_5$, giving rise to the allyl anion *(1)*, $R'=C_6H_5$.

Thus, we have been able to prepare the first trianion *(3d)*, $R'=C_6H_5$, with $Cs^{\oplus}$ as gegenions and which is stable in THF, even at room temperature[9]. The parent carbon skeleton of the trianions *(3)*, $R'=C_6H_5$, displays a further peculiarity: Since the corresponding allyl cation is also accessible[10], it can be obtained in five different oxidation states. Polarographic investigations are in progress.

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CAS Registry numbers:
(1a) (R′=H), 34631-38-4; *(1a)* ($R'=C_6H_5$), 58378-29-3; *(1b)* ($R'=C_6H_5$), 58378-30-6; *(1c)* ($R'=C_6H_5$), 66018-18-6; *(1d)* ($R'=C_6H_5$), 66018-17-5; *(2a)* ($R'=C_6H_5$), 66018-16-4; *(2b)* ($R'=C_6H_5$): 66018-15-3; *(2c)* (R′=H), 66018-14-2; *(2c)* ($R'=C_6H_5$), 66018-13-1; *(2d)* ($R'=C_6H_5$), 66018-12-0; *(3a)* ($R'=C_6H_5$), 66018-11-9; *(3b)* ($R'=C_6H_5$), 66036-84-8; *(3c)* (R′=H), 66018-10-8; *(3c)* ($R'=C_6H_5$), 66018-09-5; *(3d)* ($R'=C_6H_5$), 66018-08-4; *(4)*, 66018-07-3; *(5)*, 29882-22-2; *(5)* (deuterated), 66018-06-2; *(6)* ($E=C_2H_5$, $R'=C_6H_5$), 66018-05-1; *(6)* ($E=CH_3$, $R'=C_6H_5$), 66018-04-0; *(6)* ($E=Si(CH_3)_3$, $R'=C_6H_5$), 66018-21-1; *(7)* (E=H, $R'=C_6H_5$), 56374-49-3; *(7)* (E=D, $R'=C_6H_5$), 66018-20-0; *(7)* ($E=CH_3$, $R'=C_6H_5$), 66018-19-7

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] *G. Boche, D. R. Schneider*, Angew. Chem. *89*, 907 (1977); Angew. Chem. Int. Ed. Engl. *16*, 869 (1977).

[2] *H. H. Freedman, V. R. Sandel, B. P. Thill*, J. Am. Chem. Soc. *89*, 1762 (1967).

[3] The duration of such heterogeneous reactions depends upon the nature of the surface of the metal and the stirrer speed.

[4] a) Reaction of the olefin *(6)*, R′ = E = H, with lithium in THF at −78 °C; the intermediary radical anion dimerizes to a dianion, which is transformed by D_2O into the doubly deuterated hydrocarbon *(5)*. Protonation of this dianion and of the tetraanion *(4)* gave identical products.—b) Cf. *J. W. Burley, R. Ife, R. N. Young*, Chem. Commun. *1970*, 1256; *G. C. Greenacre, R. N. Young*, J. Chem. Soc. Perkin Trans. II *1975*, 1661.

[5] a) *A. Claus, H. Mercklin*, Ber. Dtsch. Chem. Ges. *18*, 2932 (1885).—b) From an experiment carried out by *D. R. Schneider*: Ref. [1].

[6] *J. E. Mulvaney, D. Savage*, J. Org. Chem. *36*, 2592 (1971).

[7] Reaction of the allyl anion *(1)*, R′ = C_6H_5, with two equivalents of potassium naphthalene affords the trianion *(3)*, R′ = C_6H_5, in 92% yield. Sodium and lithium naphthalene lead to 45% and 15% reduction, respectively.

[8] *W. H. Smith, A. J. Bard*, J. Am. Chem. Soc. *97*, 5203 (1975).

[9] a) Trilithium compounds: cf. *e.g. W. Priester, R. West*, J. Am. Chem. Soc. *98*, 8421, 8426 (1976); *J. J. Bahl, R. B. Bates, W. A. Beavers, C. R. Launer, ibid. 99*, 6126 (1977) and references cited therein; b) *C. F. Koelsch, ibid. 79*, 4439 (1957), prepared a trisodium compound, *E. G. Janzen, J. G. Pacifici, ibid. 87*, 5504 (1965), the corresponding tripotassium compound; c) *E. Grovenstein Jr., Th. H. Longfield, D. E. Quest, ibid. 99*, 2800 (1977), have described a dianion containing $Cs^{\oplus}$ gegenions in which both negative charges are separated from each other.
Note added in proof (March 15, 1978): 1,3-Diphenyl-2-azaallylsodium is also reduced, *e.g.* with lithium, to give the corresponding trianion. The intermediate dianion radical leads to a CC connected dimer in 10±5% yield.

[10] Warming the allyl bromide *(6)*, E = Br, R′ = C_6H_5, in cyclohexane leads to formation of 2,3-diphenylindene; the 1,2,3-triphenylallyl cation must occur as intermediate [cf. *C. F. Bergmann*, J. Org. Chem. *6*, 543 (1941)].

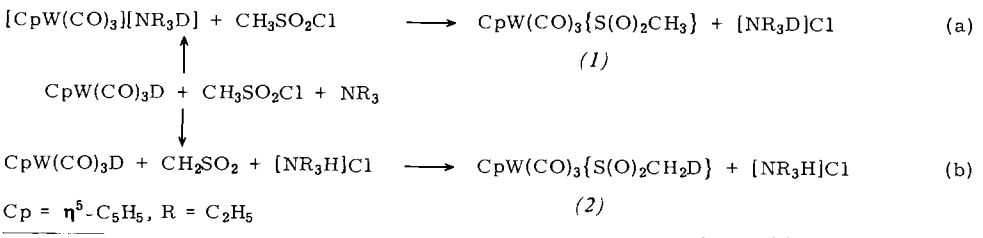
Demonstration of "Sulfene" Insertion into the Metal-Hydrogen Bond

By *Ingo-Peter Lorenz*[*]

The *S*-oxides of thiocarbonyl derivatives are of preparative and theoretical interest[1, 2]. The parent compounds $H_2C{=}SO$ and $H_2C{=}SO_2$ ("sulfine" and "sulfene") are extremely unstable and are distinguished by the numerous possible reactions which they can undergo *in situ*. A "sulfene insertion" into the metal-hydrogen bond was recently described as the first sulfene reaction in complex chemistry[3] and has now been demonstrated by D-labeling experiments.

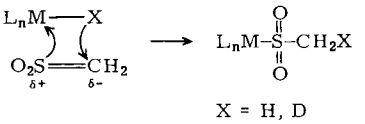
Earlier reactions of the hydrides η^5-$C_5H_5M(CO)_3H$ (M = Cr, Mo, W) with methanesulfonyl chloride[3, 4] did not lead to the desired product η^5-$C_5H_5M(CO)_3\{S(O)_2CH_3\}$, which, in the case of M = W, were formed only after addition of a tertiary amine[3]. Here, two reaction paths were possible: firstly, the stabilizing quaternization of the amine, which facilitates attack of the sulfonyl chloride; secondly participation in the reaction of sulfene (thioformaldehyde *S,S*-dioxide).

The reaction of η^5-$C_5H_5W(CO)_3D$ with CH_3SO_2Cl and triethylamine—as sulfene generator[1a]—was carried out in order to clarify the problem. Actually, only the monodeuterated methanesulfinato-*S* compound η^5-$C_5H_5W(CO)_3\{S(O)_2CH_2D\}$ *(2)*, and protonated ammonium chloride are formed. Thus the reaction path (a) *via* base-catalyzed intermolecular HCl- or DCl-elimination is ruled out, and the path (b) *via* intramolecular HCl-elimination and sulfene insertion is confirmed:



The physical properties of *(2)* resemble those of the undeuterated complex *(1)*. Composition and structure follow from elemental analysis, molecular weight determination (408, osmometric in CH_2Cl_2), and mass, IR and ^{1}H-NMR spectra. The mass spectrum (70 eV, 120 °C) shows the molecular ion at *m/e* = 413 (^{184}W) with low intensity, together with the complete series of fragment ions, and the recombination product $[\eta^5$-$C_5H_5W(CO)_3]_2$ as ion with greatest mass. In the IR spectrum (solid/KBr) a sharp band appears at 2355 cm^{-1} which is assigned to the CD stretching vibration; in the region of the terminal CO ligands there appear ν(CO) bands of the classes $A_1 + E$ or $A' + (A' + A'')$ characteristic for C_{3v}- or C_s local symmetry at 2057 (s) and 1969 (vs), 1960 (sh) cm^{-1} (in $CHCl_3$ solution) respectively; the sulfinato-*S* coupling follows from the position and frequency difference of the SO_2 stretching absorptions: $\nu_{as}(SO_2)$ at 1205 (sh), 1196 (vs) and $\nu_s(SO_2)$ at 1056 (s), 1039 (m) cm^{-1} (solid/KBr). The ^{1}H-NMR spectrum of *(2)* shows two singlets at δ = 5.84 (C_5H_5) and 2.74 (CH_2) in the correct intensity ratio ($CDCl_3$ solution, $\delta_{TMS} = 0$), that of the triethylammonium chloride arising in the formation of *(2)* shows the multiplet signals expected to appear on account of the *N*-proton.

MO-SCF-CNDO calculations for sulfene indicated extensive participation of the dipolar ylide resonance form[2a]. The resulting strong *C*-nucleophilicity and *S*-electrophilicity is apparent from the ready decomposition and pronounced reactivity of the compound. As expected, sulfene reacts with a metal-hydrogen bond to form a *sulfinato-S* complex:



The reaction mechanism is accordingly interpreted as electrophilic attack of the sulfur atom and is by no means so complicated as that of a SO_2-insertion into the metal-carbon bond[5]. The analogous reaction of sulfine (thioformaldehyde *S*-oxide) to give *sulfenato-S* complexes is presently under investigation. Both molecules and their derivatives ought also to be suitable species for the promotion of ring closure and addition reactions as well as complex stabilization[6].

Experimental

All operations must be carried out under nitrogen using anhydrous and oxygen-free solvents.

To a stirred solution of η^5-$C_5H_5W(CO)_3D$[7] (1.34 g, 4 mmol) in tetrahydrofuran (20 ml) at −40 °C is added dropwise, firstly 0.69 g (6 mmol) CH_3SO_2Cl, and then 1.65 ml (12 mmol) $N(C_2H_5)_3$. The mixture is allowed to warm to 25 °C, stirred for a further 1 h, and the suspension evaporated to dryness. The residue is taken up in *ca.* 30 ml CH_2Cl_2, and the resulting solution filtered and evaporated to dryness. After dissolution of the residue in 15 ml CH_2Cl_2 the solvent is carefully removed by passage of N_2. Orange colored needles

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are formed which are dried in a high vacuum; m. p. 173—175 °C (dec.); yield 1.0 g (60%).

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CAS Registry numbers:
(1), 52409-63-9; (2), 65915-56-2; $CpW(CO)_3D$, 65915-50-6; CH_3SO_2Cl, 124-63-0

[1] a) G. Opitz, Angew. Chem. 79, 161 (1967); Angew. Chem. Int. Ed. Engl. 6, 107 (1967); b) T. Nagai, N. Tokura, Int. J. Sulfur Chem. B 7, 207 (1972); J. F. King, Acc. Chem. Res. 8, 10 (1975).
[2] a) J. P. Snyder, J. Org. Chem. 38, 3965 (1973); b) E. Block, H. Bock, S. Mohmand, P. Rosmus, B. Soluki, Angew. Chem. 88, 380 (1976); Angew. Chem. Int. Ed. Engl. 15, 383 (1976).
[3] I.-P. Lorenz, R. Griesshammer, Z. Naturforsch. B 31, 888 (1976).
[4] M. Graziani, J. P. Bibler, R. M. Montesano, A. Wojcicki, J. Organomet. Chem. 16, 507 (1969).
[5] S. E. Jacobson, P. Reich-Rohrwig, A. Wojcicki, Inorg. Chem. 12, 717 (1973).
[6] W. Beck, private communication.
[7] Modified synthesis according to A. Davison, J. A. McCleverty, G. Wilkinson, J. Chem. Soc. 1963, 1133.

Structural Changes during the Oxidation of B-, C-, Si-, and P-Substituted Hydrazines[1, 2]

By *Hans Bock, Wolfgang Kaim, Andrzej Semkow*, and *Heinrich Nöth*[*]

Hydrazines belong to the few classes of compounds, which, despite the absence of multiple bonds, can be oxidized to stable radical cations. Energy differences and changes in electron distribution[3] accompanying these redox reactions may be discussed on the basis of photoelectron and electron spin resonance spectra (Table 1: PE- and ESR data): PE spectroscopically measurable ionizations in the gas phase occur "vertically", *i.e.* so rapidly that the molecular structure will not change, whereas oxidation in solution leads "adiabatically" to radical cations in their energetically preferred conformation.

The low N-ionization energies of the B-, C-, Si- and P-substituted hydrazines (Table 1) and their splittings $\Delta IE_{1,n}$ as a function of the dihedral angle ω between the nitrogen electron pairs n_N can be rationalized as follows: the smaller the effective nuclear charge of the substituent atom X and/or the stronger the n_N/σ_{NX} interaction, the lower the value of IE_1. The more the dihedral angle deviates from $\omega = 90°$ the more will the increased n_N/n_N interaction energetically raise the ground state of the neutral molecule M, and the more will the improved charge delocalization lower the ground state of the resulting radical cation $M^{\bullet\oplus}$. More detailed information may be gathered from the corresponding PE ionization energies: the two N-electron pair ionizations of tetramethylhydrazine are split by ± 0.28 eV about $IE_1(n_N) = 8.55$ eV of trimethylamine[4f]. Replacement of H_hC- by $(H_3C)_mSi$ substituents lowers all the N-ionization energies. The different splittings $\Delta IE_{1,n}$ for hydrazine derivatives with varying dihedral angles ω between the N-electron pairs[2, 4b, 4c] are evident: open chain derivatives with $\omega \rightarrow 90°$ display only small differences $\Delta IE_{1,2}$ while the flattened five-membered rings with $\omega \rightarrow 0°$ exhibit considerable differences $\Delta IE_{1,2}$. Among the six-membered ring derivatives with the preferred conformations

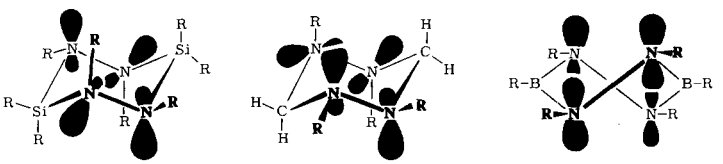
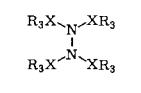
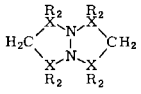
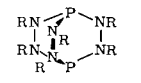


Table 1. Molecular properties of X(= B, C, Si, or P)-substituted hydrazines containing $n = 2$, 4 or 6 nitrogen electron pairs. PE data: N-ionization energies IE_n, and splitting $\Delta IE_{1,n}$ [eV]. ESR data: N-, H- and X-coupling constants a^{14}_N, $a_H^{NCH_3}$ and a_X [mT].

Compound type	XR_m	IE_1	IE_n	$\Delta IE_{1,n}$	Ref.	n	a^{14}_N	h	$a_H^{NCH_3}$	x	a_X	Ref.
	$Si(CH_3)_3$	(7.9) [a]	(8.2) [a]	≤0.3	[4a]	2	0.752	(36	0.013) [b]	4	0.16	[4a]
	CH_3	8.27	8.82	0.55	[4b]	2	1.34	12	1.27		— [c]	[5a]
	$Si(CH_3)_2$	7.15	9.00	1.85	[4a]	2	0.868	(24	0.03) [b]	4	0.5	[4a]
	CH_2	7.87	9.44	1.57	[4b]	2	1.76	8	1.56		— [c]	[5a]
	$Si(CH_3)_2$	(7.5) [a]	(8.6) [a]	≤1.1	[2]	2[e]	1.050	6	1.375	2	0.5	[2]
	CH_2	7.90	10.37	2.47	[4c]	2[e]	1.456	6	1.343		— [c]	[5b]
	BCH_3	6.83	10.15	3.32	[4d]	4	0.690	12	0.793	2	0.32	[2]
	$R = CH_3$	7.21	9.64	2.43	[4e]	6	0.402	18	0.505	2	1.9 [d]	[2]

[a] Overlapping PE bands. [b] Protons of the $Si(CH_3)_m$ groups. [c] Not observed. [d] Temperature dependent [2]. [e] The radical cation ESR spectrum shows only 2 coupling nitrogens (Fig. 1).

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the presumably[2] (*N-N*)equatorial-axial R_2Si compound shows only a small splitting; for the (*N-N*)diequatorial-(*N-N*)diaxial H_2C-derivative[6a] a considerably larger value $\Delta IE_{1,4}$ results and the four N-ionizations of the "*twist*"-tetraazadiboracyclohexane[4b] are distributed over 3.32 eV (Table 1). In the case of the bicyclic phosphane, with staggered S_6

arrangement of the methyl groups[6c], the given energy region $\Delta IE_{1,6}$ contains additionally one P-electron pair ionization[4e].

In solution, the radical cations of B-, C-, Si- and P-substituted hydrazines can be generated with $AlCl_3$ in CH_2Cl_2[2, 4a, 7]. Their ESR spectra differ considerably: Thus, that of the oxidized B_2N_4 six-membered ring expectedly exhibits its numerous lines (Fig. 1:A), whereas that of the Si_2N_4 six-membered ring unexpectedly shows only a few (Fig. 1:B).

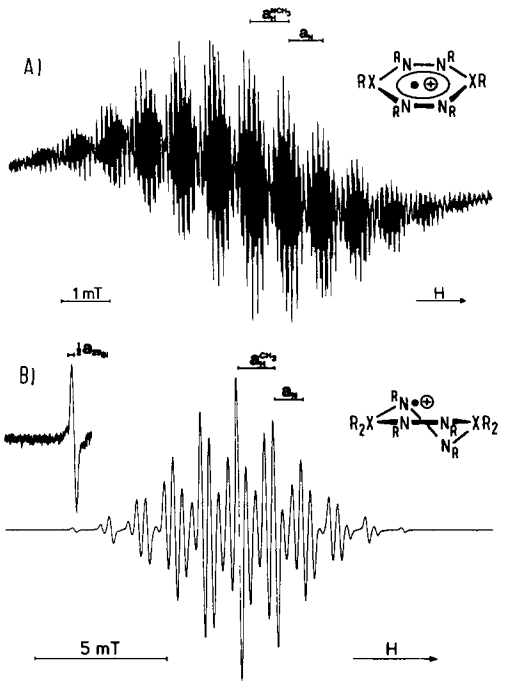
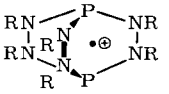


Fig. 1. Completely different ESR spectra of hydrazine radical cations may result, even if their overall topology as well as the recording conditions (T = 225 K) are similar: A) The dark-blue radical cation of hexamethyl-1,2,4,5-tetraaza-3,6-diboracyclohexane (X = B) exhibits an ESR spectrum which can be satisfactorily simulated with the quoted coupling constants of equivalent 4 N-, 12 H- and 2 B-nuclei [2]. B) The colorless radical cation of octamethyl-1,2,4,5-tetraaza-3,6-disilacyclohexane (X = Si) unexpectedly exhibits only coupling of equivalent 2 N- and 6 H-nuclei and of one ^{29}Si nucleus of natural abundance 4.7%.—The results show that within the ESR time scale of $\approx 10^{-6}$ s the spin density is distributed over both RN—NR bridges in $R_6B_2N_4^{\oplus\bullet}$ but over only one such bridge in $R_8Si_2N_4^{\oplus\bullet}$. Like the iso-π-electronic benzene radical anion; the B_2N_4 radical cation is therefore most likely planar, whereas only one of the RN—NR bridges should be flattened in the Si_2N_4 six-membered ring.

The ESR coupling constants (Table 1) assigned[2] by careful spectra simulation as well as ENDOR measurements afford, *inter alia*, the following information: The still resolved $(H_3C)_m$Si-methyl proton coupling (Fig. 1: B) confirms extensive spin delocalization (cf. *e.g.* [2, 4a]). The spin density, however, is located predominantly in the RN—NR bridges, as indicated *e.g.* by the comparably large sums of the coupling constants of the dimethylhydrazine radical cation[8a] (cf. Table 1):



$\sum_N a_{14_N}$ = 2.412 mT

$\sum_H a_H^{NCH_3}$ = 9.090 mT



$\sum_N a_{14_N}$ = 2.94 mT

$\sum_H a_H^{NCH_3}$ = 7.56 mT

In the six-membered ring derivatives, the spin density at the heteroatoms X is only low[8b]; that in each of the individual RN—NR bridges is of comparable size (Table 1). The differing spin distribution over one, two or three RN—NR bridges are rather due to steric effects (Fig. 1 and Table 1). Thus, in the case of the C- and Si-tetraazacyclohexane radical cations a boat conformation at the R_2X groups is sterically as disadvantageous as a rapid spin exchange between the different types of RN—NR bridges *via* transition of one "half-chair" conformation into the other. On the contrary, the trigonal planar arrangement of the $RB(NR—)_2$ halves favors flattening of the B_2N_4 six-membered ring.

From the PE and ESR data (Table 1) it follows that the hydrazine radical cations investigated are stabilized by planarization. In the case of unsubstituted $N_2H_4^{\oplus\bullet}$ this is reflected by an INDO open-shell hypersurface[9] whose total energy minimum is calculated for a completely planar structure (cf. Fig. 2).

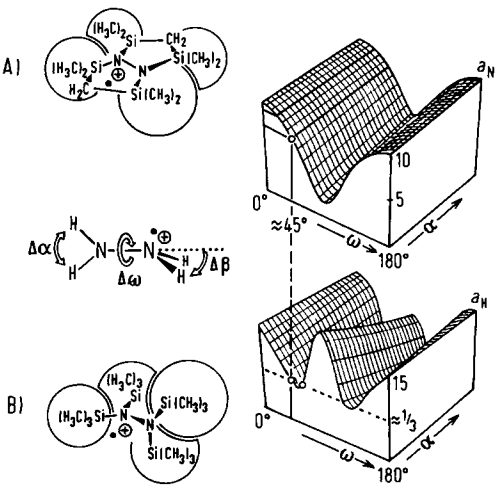
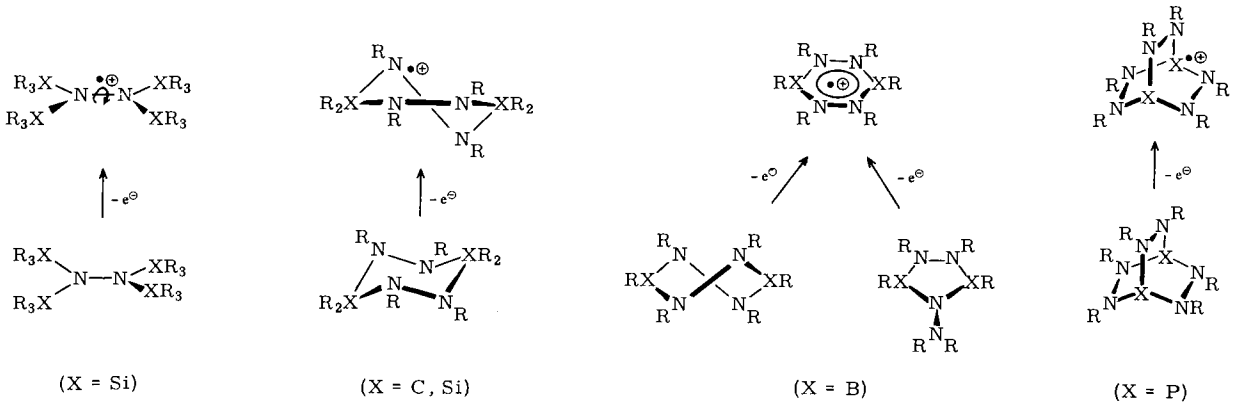


Fig. 2. For the hydrazine radical cation $H_2N—NH_2^{\oplus\bullet}$, INDO open-shell calculations [9] predict a minimum on the total energy hypersurface for planar geometry (D_{2h}). Additionally calculated coupling constants depend predominantly on the dihedral angle ω: on twisting to ω = 90°, the coupling constant a_{14N}^{INDO} reaches a minimum (A), a_H^{INDO} a maximum (B). Comparison with the measured ESR data a_{14N} and a_{29Si} (Table 1)—in the silylated hydrazines Si is adjacent to N—provides information on the structure of the oxidation product in solution: starting from the presumably planar bicyclic tetrasilylhydrazine radical cation, the three-dimensional a_X^{INDO} tables yield a dihedral angle ω ≈ 45° for the open chain tetrakis(trimethylsilyl)hydrazine radical cation, both from the difference $\Delta a_{14N} = 8.62 - 7.52 = 0.9$ mT (A) as well as from the ratio $a_{29Si}^{chain}/a_{29Si}^{ring} = 1.6/5.0 \approx 1/3$ (B). Apparently, the bulky $(H_3C)_3Si$-substituents prevent the energetically favored complete planarization of the $X_2N—NX_2^{\oplus\bullet}$ skeleton.

Comparison of the ESR data of tetrasilylated hydrazine radical cations (Table 1) based on the calculated coupling constants a_X^{INDO}, suggests for the open-chain oxidation product in solution a structure with reduced dihedral angle (Fig. 2: a_N and a_H). The energetically favorable complete planarization is obviously prevented by the bulkiness of the $(H_3C)_3Si$ substituents.

Altogether, the following structural changes are observed during the oxidation of B-, C-, Si- and P-substituted hydrazines:



(X = Si) (X = C, Si) (X = B) (X = P)

The remarkable stability of the dark blue radical cation $R_6B_2N_4^{\oplus\bullet}$ with a planarized 7π-electron system is underlined by the fact that the ESR spectrum of the six-membered cyclic radical cation (Fig. 1: A) is also recorded on oxidation of the isomeric R_2N-substituted five-membered ring.

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German version: Angew. Chem. 90, 308 (1978)

[1] Radical Cations, Part 17; and Contributions to the Chemistry of Boron, Part 97. Parts 16 and 96, respectively: *H. Bock, W. Kaim, N. Wiberg, G. Ziegleder*, Chem. Ber., in press, and *H. Fussstetter, N. Nöth, ibid.*, in press.

[2] Part of the Dissertation by *W. Kaim*, Universität Frankfurt 1977.

[3] Cf. *H. Bock*, Angew. Chem. *89*, 631 (1977); Angew. Chem. Int. Ed. Engl. *16*, 613 (1977); and references cited therein.

[4] a) *H. Bock, W. Kaim, J. W. Connolly*, Angew. Chem. *88*, 766 (1976); Angew. Chem. Int. Ed. Engl. *15*, 700 (1976); b) *S. F. Nelsen, J. M. Buschek*, J. Am. Chem. Soc. *96*, 2392, 6982, 6987 (1974); c) *P. Rademacher*, Tetrahedron Lett. *1974*, 83; d) *J. Kroner, D. Nölle, H. Nöth, W. Winterstein*, Z. Naturforsch. *B29*, 476 (1974); e) *A. H. Cowley, D. W. Goodman, N. A. Kuebler, M. Sanchez, J. G. Verkade*, Inorg. Chem. *16*, 854 (1977); f) cf. *H. Bock*, Pure Appl. Chem. *44*, 343 (1975); and references cited therein.

[5] a) *S. F. Nelsen, G. R. Weisman, P. J. Hintz, D. Olp, M. R. Fahey*, J. Am. Chem. Soc. *96*, 2916 (1974); b) *S. F. Nelsen, P. J. Hintz, J. M. Buschek, G. R. Weisman, ibid. 97*, 4933 (1975).

[6] a) *R. A. Y. Jones, A. R. Katritzky, R. Scattergood*, Chem. Commun. *1971*, 644; b) *H. Fussstetter, J. W. Huffmann, H. Nöth*, Z. Naturforsch. *B31*, 289 (1976); c) *W. van Doorne, G. W. Hunt, R. W. Perry, A. W. Cordes*, Inorg. Chem. *10*, 2591 (1971).

[7] Cf. *e.g.* a) *H. Bock, G. Brähler, G. Fritz, E. Matern*, Angew. Chem. *88*, 765 (1976); Angew. Chem. Int. Ed. Engl. *15*, 669 (1976); b) *H. Bock, W. Kaim*, Tetrahedron Lett. *1977*, 2343; c) *H. Bock, W. Kaim, H. E. Rohwer*, J. Organomet. Chem. *135*, C 14 (1977).

[8] a) *P. Smith, R. D. Stevens, R. A. Kaba*, J. Phys. Chem. *75*, 2048 (1971); b) Calculation with the isotropic hyperfine coupling constants $A_B^{iso} = 72.0$, $A_{Si}^{iso} = 120.8$ or $A_P^{iso} = 363.6$ mT gives total (s)-nuclear spin densities $\rho_X(o) = a_X A_X^{iso}$ for the six-membered ring derivatives $\rho_B(o) = 0.0089$, $\rho_{Si}(o) = 0.0083$ and $\rho_P(o) = 0.0105$.

[9] The computer program contains a Davidson-Fletcher-Powell subroutine, which has been used for optimization of the N—N bond length. The coupling constants were calculated with the hyperfine constants $Q_N = 53.9864$ and $Q_H = 37.9356$ mT.

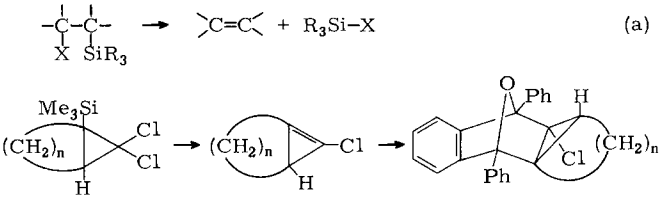
ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

The mechanism of biological methylation of metals is examined by *J. M. Wood, A. Cheh, L. J. Dizikes, W. P. Ridley, S. Rackow*, and *J. R. Lakowicz*. Mercury pollution has directed interest to biogenic organometallic compounds. Such compounds readily accumulate in tissues and are poisonous, usually towards the central nervous system. Alkylmetal compounds stable towards water and formed biologically are known for Hg, Sn, As, Se, Te, Pd, Au, Tl, and Pb. The main emphasis of the article is on the mechanisms of formation, especially for those elements which are widespread in the biosphere. [Mechanisms for the Biomethylation of Metals and Metalloids. Fed. Proc. *37*, 16—21 (1978); 41 references]

[Rd 12 IE]

Alkene synthesis *via* β-functionalized organosilicon compounds is the subject of a review by *T. H. Chan*. The synthetic potential of reaction (a), first reported some 30 years ago, has only recently been recognized. The method has proved very suitable for the synthesis of α,β-unsaturated esters, aldehydes, and nitriles. In addition, strained and very reactive alkenes have



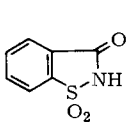
(a)

(1), n = 4,5,6

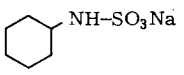
nitriles. In addition strained and very reactive alkenes have also been prepared in this way, *e.g.* cyclopropenes and the "anti-Bredt alkene" *(1)* having a bridgehead double bond. [Alkene Synthesis *via* β-Functionalized Organosilicon Compounds. Acc. Chem. Res. *10*, 442—448 (1977); 66 references]

[Rd 3 IE]

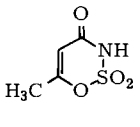
The properties and syntheses of sweeteners are surveyed by *B. Crammer* and *R. Ikan*. The search for an ideal artificial sweetener is difficult because there is still no satisfactory correlation between molecular structure and the sensation of sweetness. Not only saccharin *(1)*, cyclamate *(2)*, and oxathia-



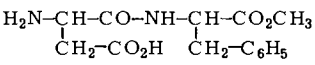
(1)



(2)



(3)



zinone dioxides such as *(3)* taste sweet, but so does the dipeptide aspartame (L,L form), to say nothing of cane sugar and other natural products. Discoveries of new artificial sweeteners still depend largely upon chance. [Properties and Syntheses of Sweetening Agents. Chem. Soc. Rev. *6*, 431—465 (1977); 107 references]

[Rd 5 IE]

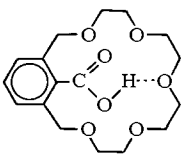
The relationship between steroid hormones and the growth and development of plants is considered by *J. M. C. Geuns*. It has long been known that steroid hormones of animal origin can stimulate plant development and growth and are metabolized by plants. Recently, steroid hormones and related compounds have been isolated from plants, *e.g.* sex hormones, corticoids, pentacyclic triterpenoids, saponins, digitonin, and tomatin. Although biological activity has been proved, it is difficult to quantify because steroids dissolve poorly and nonreproducibly in aqueous media. [Steroid Hormones and Plant Growth and Development. Phytochemistry *17*, 1—14 (1978); 156 references]

[Rd 11 IE]

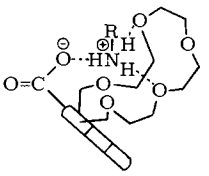
Prediction of the spatial structure of a protein from the amino acid sequence is possible in principle. *M. J. E. Sternberg* and *J. M. Thornton* consider the various approaches to this goal. The main problem is the large number of possibilities: a small protein with only 50 amino acids can exist in some 10^{50} different conformations. The predictions concentrate mainly upon the secondary structure of the amino acid chains and how the natural folding processes could proceed. Use is made of simple models for the conformation of the protein and of energetic aspects of interatomic interactions. [Prediction of Protein Structure from Amino Acid Sequence. Nature *271*, 15—20 (1978); 59 references]

[Rd 6 IE]

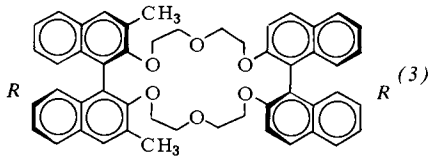
The design of host-guest complexes with synthetic hosts is the topic of an article by *D. J. Cram* and *J. M. Cram*. These complexes can be regarded as models for enzyme-substrate complexes. A typical example is the crystalline complex *(2)* formed from the host *(1)* and the *tert*-butylammonium ion. The structure of *(2)* has been established by X-ray methods. The incorporation of steric barriers endows the host molecule with the ability to recognize structures. Optically active hosts such as *(3)* are capable of chiral recognition and can remove one enantiomer preferentially, *e.g.*, from a mixture of enantiomeric salts of primary amines. [Design of Complexes between Synthetic Hosts and Organic Guests. Acc. Chem. Res. *11*, 8—11 (1978); 28 references]



(1)



(2)



(3)

[Rd 7 IE]

Conformational studies on hexahydropyridazines are considered by *S. E. Nelsen*. Compounds such as the 1,2-dimethyl derivative *(1)* are good models for quantitative studies on the influence of the dihedral angle θ between the lone pairs on conformational equilibria and rate constants. A value of $\theta = 90°$ is preferred in many compounds with neighboring hetero atoms (*gauche* effect). *(1ee)* ($\theta \approx 180°$) appears to be ruled out; however, *(1ae)* and *(1aa)* ($\theta \approx 60°$) are sterically destabilized by axial substituents. Interconversions of the conformers of *(1)* and similar compounds have been examined above all by PE and ^{1}H- and ^{13}C-NMR spectroscopy, cyclic voltammetry at low temperatures, and dipole moment measurements. [Conformational Studies of Hexahydropyridazine Derivatives. Acc. Chem. Res. *11*, 14—20 (1978); 38 references]



(1ee) *(1ae)* *(1aa)*

[Rd 8 IE]

The physical characterization of cytoplasmatic gluco- and mineralosteroid receptors is reviewed by *M. K. Agarwal*. Lipophilic steroid molecules are assumed to migrate through the cell membrane and to encounter a receptor of high affinity (K_d *ca.* 10^{-10} mol/l) and low capacity in the cytoplasm. While the receptor appeared to be homogeneous on density gradient centrifugation and gel filtration, chromatography on ion exchangers showed it to consist of proteins which are heterogeneous with regard to their charge. It remains to be established why receptors are so labile *in vitro*, how the receptor-hormone complex permeates the nuclear membrane, and how it interacts with a likewise still hypothetical acceptor in the nucleus. [Physical Characterization of Cytoplasmatic Gluco- and Mineralo-Steroid Receptors. FEBS Lett. *85*, 1—8 (1978); 54 references]

[Rd 10 IE]

BOOK REVIEWS

Electron Spectroscopy: Theory, Techniques, and Applications. Vol. 1. Edited by *C. R. Brundle* and *A. D. Baker*. Academic Press, Inc., London—New York 1977. xv, 459 pp., various figs. and tables, bound, $ 46.90.

Although photoelectron spectroscopy began really to flourish only in 1970 with the advent of commercial spectrometers, this spectroscopic method has now become so widely diversified that a series of volumes must be planned if the various

types and applications of (photo)electron spectroscopy are to be brought again under one roof. The editors promise that this will result in cross-fertilization of the experimental and theoretical approaches.

After a general introduction to photoelectron spectroscopy by the editors, *R. L. Martin* and *D. A. Shirley* describe in Chapter 2 some aspects of the theory of photoemission and *W. L. Jolly* explains the model ideas used in the field of X-ray photoelectron spectroscopy of inorganic substances (Chapter 3). In the following Chapters 4 to 6 *W. C. Price* (small molecules), *E. Heilbronner* and *J. P. Maier* (organic molecules), and *R. L. Dekock* (inorganic molecules) devote themselves to the possible applications of UV photoelectron spectroscopy in the gas phase. Chapters 7 and 8, on high-temperature UPS investigations *(J. Berkowitz)* and coincidence experiments *(M. E. Gellender* and *A. D. Baker)* put the reader in touch with special techniques of current UV photoelectron-spectroscopic research.

The following sections can be particularly recommended: Chapter 1; the considerations in Chapter 2 on the influence of relaxation and correlation on ionization cross-sections; the discussions in Chapter 4 on the intensity of photoelectron spectra; the presentation of theory, experimental aspects, and band assignment in Chapter 6, the clear description of the angular distribution of photoelectrons in Chapter 7; and the explanation of the connections between resolution and signal intensity in one- and two-parameter measurements in Chapter 8. In addition, the individual chapters afford an insight into the special types of research and photoelectron-spectroscopic viewpoints of the authors. All in all, the reviewer has had great pleasure from this volume and can heartily recommend it to every chemist interested in photoelectron spectroscopy.

Armin Schweig [NB 407 IE]

Gedächtnis und Lernen in psychologischer Sicht (Memory and Learning from the Psychological Point of View). Vol. I. Biologie des Lernens (Biology of Learning). Vol. II. By *H.-J. Flechtner*. S. Hirzel Verlag, Stuttgart 1976. Vol. I: 2nd Edit., x, 354 pp., 5 figs., paperback, DM 25.00; Vol. II: 1st Edit., xii, 483 pp., 34 figs., paperback, DM 25.00.

The author's original aim was to write a "Biochemistry of Memory", but he collected so much material that a third volume, "memory", still has to appear.

The material is presented from the psychological and neurological points of view. According to *Mandell*, the course of development of neurophysiology shows a "shift from electricity to juice". About 100 pages of the first volume are devoted to definitions and the description of problems, while the other 250 pages deal with learning. The objective school in psychology is presented in a historical treatment. There is a clear account of how *Bechterew*'s and *Pavlov*'s reflexology gave rise to behaviorism. Concepts like operant conditioning and positive or negative reinforcement, which are associated with *Thorndike* and *Skinner*, are necessary for understanding thought processes. The chapter entitled "Psychology of Learning" describes storage, recall, forgetting, and unlearning.

The chapters in the second volume are called "Fundamentals", "Localization of Learning", "Assimilation and Processing", "Engrams", and "Learning and Having Learned". These deal with the morphological, chemical, and biochemical aspects needed for understanding the way the nervous system operates.

What is confusing is that the numbered references appearing in the footnotes (in Vol. I alone 1–499) are not given under the same numbers at the end of the book (294 references in vol. I and 422 in vol. 2). Footnotes like "a. a. O. S. 73" make things even more difficult, and the frequently used abbreviations, like TrmS for transmitter substance and SgS for situation stimulus, should have been listed at the beginning. However, the reader will find a great deal of valuable information in these two volumes.

Götz F. Domagk [NB 401 IE]

Fundamentals of Integrated GC-MS. Chromatographic Science Series, Vol. 7. By *B. J. Gudzinowicz, M. J. Gudzinowicz,* and *H. F. Martin.* Marcel Dekker, Inc., New York—Basel 1976. Part I: Gas Chromatography. vii, 382 pp., numerous figs. Sfr. 124.—; Part II: Mass Spectrometry. vii, 326 pp., numerous figs., Sfr. 117.—.

The first two parts of the three-part work (the third part on the GC-MS combination has not yet appeared) are concerned in almost epic form with mainly theoretical aspects of gas chromatography and mass spectrometry.

Poorly selected practical examples with page-long reproduction of original tables without critical discussion or authors' opinion appear to be arbitrarily chosen. Outdated methods, *e.g.* the introduction of liquid samples into the mass spectrometer through a gallium sinter (Part II, pp. 23—25), are described at length, while the important application of glass capillaries in investigations of scarcely volatile substances and problems connected therewith are hardly touched upon. One gains the impression that the authors have indeed collected much of the older literature, but themselves have not the experience and above all the ability to make critical evaluations. Otherwise we would not have, for example, formulas featuring oxygen atoms with nine electrons (Part II, p. 123), to select only one crass example. Purchase of these two volumes cannot be recommended.

Gerhard Spiteller [NB 416 IE]

Gas-Solid Reactions. By *J. Szekely, J. W. Evans,* and *H. Y. Sohn.* Academic Press, New York 1976. 1st Edit., xiii, 400 pages, bound, $ 39.50.

The aim of this book is to give an introduction into the technique of gas-solid reactions.

The work is divided into eight chapters; the first is an introductory one and the second deals with mass and heat transfer for a single core in a gas stream and with diffusion processes in the pore system of a solid. It also surveys the microkinetics of heterogeneous chemical reactions and discusses reaction-induced changes in the structures of solids.

The third chapter gives a detailed account of the way a reaction proceeds on a nonporous single core in a gas stream, and introduces the "shrinking-core" model.

The fourth chapter is devoted to reactions of porous solids, and the authors discuss here separately the reactions that lead to complete vaporization of the solid and reactions that give solid end products.

The fifth chapter deals with solid-solid reactions in which a gaseous intermediate is formed.

The sixth chapter describes both some experimental techniques important in the investigation of gas-solid reactions and some of their applications. We find here an account of methods for measuring reaction rates, characterizing porous solids, and determining diffusion coefficients and effective diffusion coefficients.

The findings established for the single core are extended to fixed and fluidized-bed reactors in the seventh chapter.

The eighth and final chapter deals with gas-solid reactions of major industrial importance, such as the blast-furnace process and the gasification of coal.

Each chapter includes a long list of references covering the literature up to 1974. The value of the book is enhanced by the many figures, diagrams, and tables correctly fitted into the text. The worked examples in the individual chapters facilitate understanding of the material.

The book is a readable and comprehensive survey of the technique of gas-solid reactions, and is recommended to anyone who wants to understand this field.

Rainer Moormann [NB 402 IE]

Modern Practice of Chromatography. By *R. L. Grob*. John Wiley & Sons, Ltd., New York—London 1977. 1st Edit., xv, 654 pp., numerous figs., bound, £ 16.00.

This work, edited by *Robert L. Grob*, is the most comprehensive existing collection of contributions on the applications of gas chromatography. The individual chapters, written by experienced specialists, describe in three main parts (and in great detail, but not always with consideration of the most recent literature—capillary gas chromatography is mentioned only marginally in the theoretical part) the theory, the technology, and the applications of gas chromatography. About two-thirds of the volume are devoted to theory, qualitative and quantitative analysis, description of apparatus, procedures for sample injection, detectors, and computers. This is the first book to collect so completely such a large number of new technical developments. Emphasis should be laid on the chapters about detectors, instrumentation, and data collection; great advances have been made in recent years in these areas. The chapter dealing mainly with applications includes trace analysis (environmental analysis), examination of foods, clinical analysis, and analysis of drugs, for which work standard methods have been worked out for preparation of the samples and formation of derivatives as well as standardized conditions for separations; therein lies the particular value of this section. Minor redundancies have not been wholly avoided in the text.

The book is supplemented by a chapter on physicochemical applications of gas chromatography, where the posssible application of gas chromatography to the determination of thermodynamic quantities is pointed out, a feature rarely known to the analyst and yet of great interest.

This volume, well worth its price, offers the user of gas chromatography in a wide range of fields a wealth of experience and stimulation.

Wilfried A. König [NB 412 IE]

Structure-Solubility Relationships in Polymers. Edited by *F. W. Harris* and *R. B. Seymour*. Academic Press, New York 1977. 1st Edit., xiii 271 pp. bound, $ 13.00.

A symposium with the same title was held by the American Chemical Society—their 172nd—between August 30 and September 3, 1976. The revised and shortened versions of 21 lectures delivered there were collected in book form and printed by Academic Press Rapid Reproduction. This has given us a book which is up to date and gives a representative cross-section of research in this field.

The summarizing contributions have retained their lecture character; modern solubility theories are discussed in conjunction with the experimental results in easily comprehensible form, and at the same time more emphasis is placed on outlining the problems involved, thus making them also accessible to those who do not work in this field. In addition, the large number of references listed make further reading possible.

The authors work in a variety of places, ranging from industrial laboratories to universities, and therefore some of the polymers discussed are unusual as model substances. This is an advantage for the reader, because he can follow the development of the problem and treatment from the specific characteristics of the polymer in question.

The editors have succeeded in giving a picture of current knowledge in a limited space. From the very beginning, the book is suitable for the interested reader who works with polymers in general, while for the specialist it presents a broad basis for future research.

K. C. Berger [NB 404 IE]

Blutzuckersenkende Sulfonamide – Standort der modernen Substanzen im Vergleich zu älteren Antidiabetika (Hypoglycemic Sulfonamides—Status of Modern Substances Compared with Older Antidiabetic Agents). By *E. Haupt*. Verlag Chemie, Weinheim—New York 1977. 1st edit., viii, 169 pp., 58 figs., 3 tables, boards, DM 34.—.

The author's Habilitation Thesis, now presented in book form, is an attempt to define the position of hypoglycemic sulfonamides on the basis of pharmacodynamic, clinical, and experimental-clinical investigations. The history of the discovery and development of this class of substances is reported in an introductory chapter, where, however, the important development work carried out during 1951—1953 at the Leipzig and Jena university clinics (literature in *A. Kleinsorge*, Dtsch. Med. Wochenschr. *101*, 467 (1976)) was conspicuous by its absence.

The following sulfonylurea derivatives were investigated in the present study: tolbutamide, glibornuride, glisoxepide, and glibenclamide. The important results include the following: no differences were noticeable on oral administration in the kinetics of insulin secretion or in the course of the blood sugar curves; these findings apply both to healthy subjects and to diabetics. Secondary failure of the sulfonylurea monotherapy occurred to the same extent with all the derivatives studied; the "younger-generation" preparations active in milligram doses did not differ in this respect from the older substances. Secondary failure occurred mostly in patients who were severely overweight. The time at which failure occurs depends on the duration of the diabetes therapy and not on the time of appearance of the diabetes mellitus. Each year 5—10 % of all treatments must be broken off because of secondary failure. In the pharmacological investigations, glibenclamide given intravenously had a different effect from the other substances: it induced a distinct insulin secretion, of delayed onset and long duration, with corresponding later decrease of blood sugar (this effect occurred in both healthy and diabetic persons). It is still unclear why the action of glibenclamide is "tolbutamide-like" on oral administration and "glibenclamide-like" when injected intravenously. The difference from literature findings that indicate specific glibenclamide action also by the oral route still requires explanation (cf. *S. Raptis et al.*: 8th Kongr. Dtsch. Diab. Ges., Munich 1973).

Clinical importance attaches to the discussion of the problem of secondary failure; it confirms the finding that the insufficiency of pancreatic β cells, at first incomplete, later becomes complete. An appeal is made to diabetics specialists in clinical and general practice to compensate patients under positive long-term treatment with weight reduction, so that the secondary failure may be delayed.

Those interested in this book will be especially doctors and chemists concerned with sulfonylurea derivatives in industrial and other research laboratories.

Friedrich Willig [NB 415 IE]

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Synthesis and Biological Properties of Prostaglandin Endoperoxides, Thromboxanes and Prostacyclins

By K. C. Nicolaou, G. P. Gasic and W. E. Barnette[*]

Dedicated to Professor E. J. Corey on the occasion of his 50th birthday

Prostaglandins continue to be a major and fast-developing area of research in the chemical and biological sciences. Increasing evidence has recently prompted some researchers to suggest that the important physiological actions of these hormones are exerted by their unstable arachidonic acid pathway intermediates, the endoperoxides, thromboxanes, and prostacyclin. The importance of these substances in physiology and medicine and the challenge they pose to synthetic chemistry place them in the forefront of chemical and biochemical investigation. Current biological research has greatly benefited by synthetic advances which have made available large quantities of some of these naturally occurring intermediates and several analogs with increased stabilities. Following a brief review of the primary prostaglandins, the present article describes recent biosynthetic developments, partial and total syntheses of prostaglandin endoperoxide analogs, thromboxane B_2, and prostacyclins, and the biological properties of these molecules.

1. Introduction

Prostaglandins (PG), naturally occurring unsaturated hydroxylated fatty acids with a prostanoid 20-carbon skeleton, have been implicated as local hormones in a multitude of important physiological processes[1–4]. Amongst their ranks these substances boast of very beneficial members, such as prostacyclin, which appears to inhibit thrombus formation, while the elevated levels of other members may be harmful, for example causing pain and inflammation. Since their discovery, rapidly expanding research has thrust prostaglandins into the forefront of attention and future research may apply the acquired knowledge to such areas in medicine as thrombosis, asthma, gastric ulceration, blood pressure regulation, inflammation, and shock. A large share of the credit for the development of this field must be given to the chemists who elucidated the structures of the known prostaglandins, synthesized them, and are continually preparing new analogs which facilitate physiological research and may prove pharmacologically useful.

Their history dates back to more than forty years ago when *U. S. von Euler* and *M. Goldblatt* independently discovered a new factor, present in genital glands and human semen, which displayed vasodepressor and smooth muscle stimulating activity[5, 6]. *Von Euler* showed that the biological activity was due to a lipid soluble material with acidic properties and provisionally termed it "prostaglandin". Almost three decades elapsed between the discovery of the biological activity associated with prostaglandins and the structural elucidation of two of them. Hampered by technical difficulties in the isolation of prostaglandins and interest in other natural products such as antibiotics and steroids, investigation remained dormant for a long time. In 1960, *Bergström* and *Sjövall* isolated the crystalline PGE_1 and $PGF_{1\alpha}$ from sheep seminal vesicles[7]. Within a few years, *Bergström* and his students isolated and

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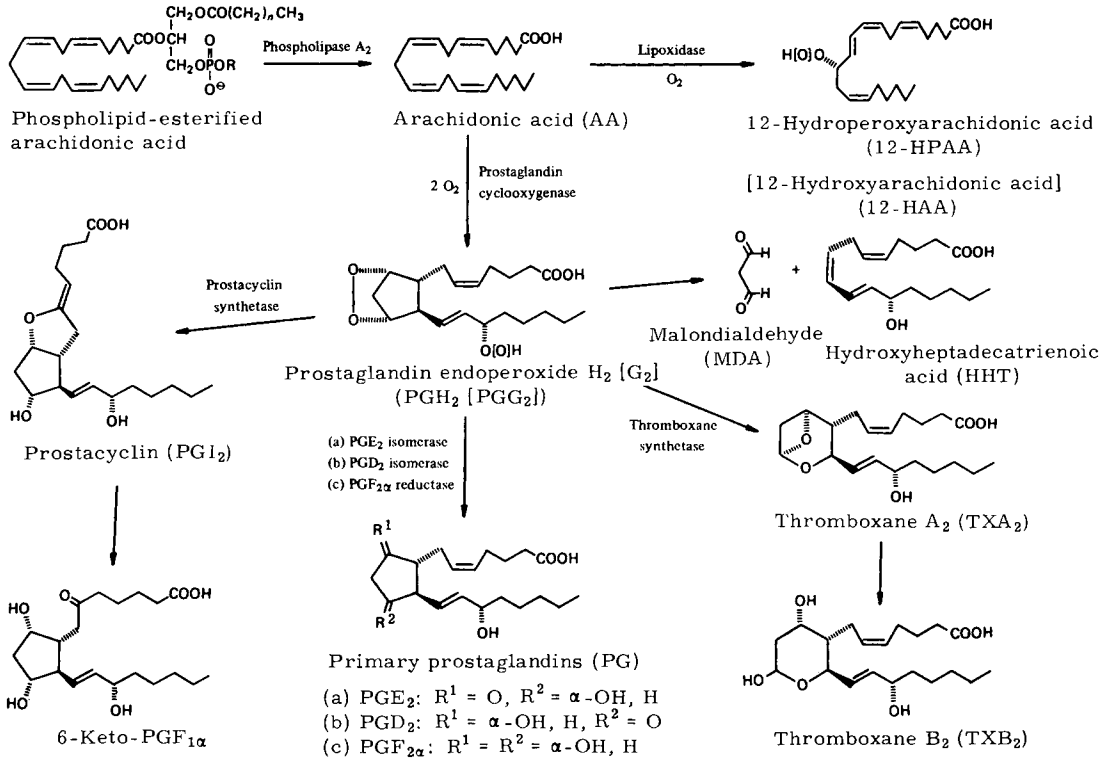


Fig. 1. The arachidonic acid peroxidation pathways: Biogenetic relationship between arachidonic acid and prostaglandin endoperoxides, prostacyclin, prostaglandins and thromboxanes.

elucidated the structure of thirteen different prostaglandins[8,9]. It was at this point, when the isolation and structural determination proved that prostaglandins were responsible for the observed biological activity, that the field came to life.

The next advance came in the biological area. *Bergström*'s group[10] and *Van Dorp*'s group[11] simultaneously demonstrated that these compounds were biosynthesized from polyunsaturated fatty acids (*e.g.* arachidonic acid, Fig. 1). *Anggärd* and *Samuelsson*[12] showed that guinea pig lung homogenates incubated with arachidonic acid simultaneously produced $PGF_{2\alpha}$ and PGE_2 without interconversion. Further work in *Samuelsson*'s laboratory led to the discovery that the oxygens attached to C-9 and C-11 originated from the same molecule of oxygen, and that an endoperoxide was the likely intermediate[13]. Despite the extensive research conducted in *Samuelsson*'s and *Van Dorp*'s laboratories, it was not until 1973 that *Samuelsson* isolated the endoperoxide intermediate, PGH_2[14,15]. Subsequently, an additional endoperoxide with a hydroperoxy group at the C-15 position was isolated and named PGG_2[15,16]. The isolation of the endoperoxides was achieved by blocking the isomerase enzyme with mercury(II) *p*-hydroxybenzoate and rapid extraction to remove them from the aqueous environment. In contrast to the previously discovered prostaglandins, the endoperoxides have a short half-life of about five minutes in biological (aqueous) systems.

In the meantime, synthetic chemists launched an all out attack on these molecules. The first total syntheses of prostaglandins started to appear in the late 1960's and by the early 1970's these highly desirable substances became relatively abundant by total synthesis. Professor *E. J. Corey* of Harvard University, whose name became almost synonymous with prostaglandins, undoubtedly deserves the most credit for the synthetic work in this area. Indeed, his syntheses are among the first, the most elegant and most practical routes to prostaglandins. A great plethora of other routes and analogs soon became available. In fact, so much synthetic work has been done in the prostaglandin area that the verb "to prostaglandize" has humorously been introduced by prostaglandin chemists to mean "to beat something to death!" A number of reviews on the synthesis of the primary stable prostaglandins are already in the literature[17] and it is not the intention of this article to deal with these works.

With the finding that the effects of the endoperoxides on airway and vascular smooth muscle were considerably greater than PGE_2 and $PGF_{2\alpha}$, the attention in research has shifted from the relatively stable prostaglandins to the unstable arachidonate pathway (Fig. 1) intermediates[18]. Interest in these intermediates was further enhanced by the observation that the endoperoxides possessed the ability to induce rapid and

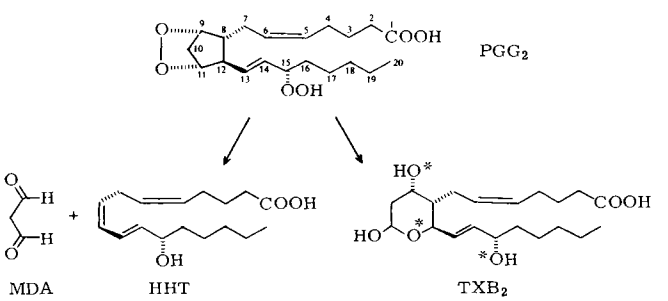


Fig. 2. Major metabolites of prostaglandin G_2 (PGG_2) in platelets: malondialdehyde (MDA), 12-hydroxy-5,8,10-heptadecatrienoic acid (HMT) and thromboxane B_2(TXB_2).

irreversible aggregation of platelets, an activity not shared by their stable counterparts[14, 16]. Several stimuli of platelet aggregation (collagen, thrombin, ADP) activate an endogenous platelet phospholipase which releases esterified arachidonic acid[19]. This free acid is instantaneously peroxidized by lipoxidase and cyclooxygenase enzymes which utilize molecular oxygen. The physiological importance of the endoperoxides, produced by platelet cyclooxygenase, has been established, since a mild hemostatic defect in a patient was found to be due to a platelet cyclooxygenase deficiency[20].

In 1969 *Piper* and *Vane*[21] described the release of a rabbit aorta contracting substance (RCS) from guinea pig lung, but again several years elapsed (1975) before *Samuelsson et al.* identified this extremely unstable molecule[22]. Two acids, thromboxane B_2(TXB_2) and 12-hydroxy-5,8,10-heptadecatrienoic acid (HHT), and malondialdehyde (MDA) were found to be the major metabolites of PGG_2 when incubated with human platelets[23, 24] (Fig. 2). Incubation of arachidonic acid with platelets under $^{18}O_2$ led to the formation of thromboxane B_2(TXB_2) labeled with ^{18}O in the three positions shown in Figure 2. In the conversion of PGG_2 to thromboxane B_2 in platelets, an extremely unstable intermediate (thromboxane A_2 $(TXA)_2$, $t_{1/2} = 30$ s) with properties similar to *Vane*'s RCS was detected by trapping experiments (Fig. 3). Thus, methanol, ethanol, or sodium azide competed with H_2O to afford the thromboxane B_2 derivatives with the hemiacetal hydroxyl group substituted by methoxy, ethoxy and azido groups, respectively. These data are in agreement with the strained bicyclic structure assigned to thromboxane A_2, which is expected to be very susceptible to nucleophilic attack at the acetal carbon to yield thromboxane B_2 or its derivatives (Fig. 3). This thromboxane A_2 structure is also in agreement with the findings that the carbon 5,6,8,9,11,12,14,15 hydrogens of arachidonic acid and PGG_2 are retained in the conversion to thromboxane B_2. Furthermore, addition of CH_3OD to platelets incubated with arachidonic acid led to the formation of mono-*O*-methylthromboxane B_2 lacking a *C*-bound deuterium atom. Therefore, the dihydropyran structure A (Fig. 3) can be excluded. Similarly, the carbonium ion B can be excluded due to its expected extremely short lifetime in aqueous medium. With the entry of thromboxane A_2 into the class of unstable intermediates (Fig. 1) the question arises as to which physiological effects are caused by endoperoxides and which are caused by thromboxanes.

However, endoperoxides are not solely converted to thromboxanes, since *Vane et al.* recently discovered that a microsomal fraction of arterial walls transforms endoperoxides into an unstable, hitherto unknown substance initially designated as PGX[1]. This latest prostaglandin was subsequently renamed PGI_2 (cf. Fig. 14) at the 1977 Prostaglandin Conference in Vail (Colorado). In most respects, its biological activity is the opposite of thromboxane A_2, inducing potent inhibition of platelet aggregation and smooth muscle relaxation. The enzyme which generates PGI_2 predominates in vascular tissue[25]. Its formation by cultured endothelium is inhibited by several fatty acid hydroperoxides (*e. g.* 15- and 12-hydroperoxyarachidonic acids, derived from platelets, see Fig. 1)[26–28].

Although the structure of this arachidonic acid pathway metabolite was postulated by *Pace-Asciak* and *Wolfe*[29] in 1971, the chemical structure of this potent inhibitor of platelet aggregation was just recently identified by *Johnson et al.*[30]

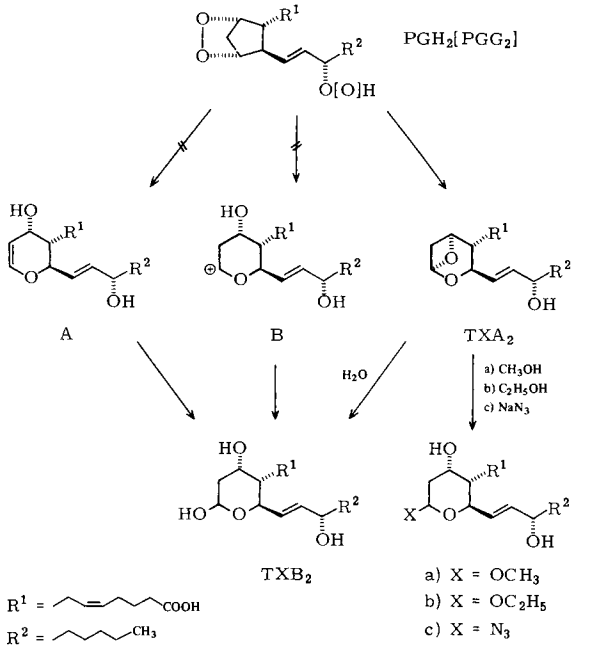


Fig. 3. Thromboxane A_2(TXA_2): Structural assignment and occurrence in metabolism.

and *Corey et al.*[31] (Fig. 4). Since the structure contains a second ring system, the name "prostacyclin" was adopted. Prostacyclin is rather unstable in aqueous, acidic or neutral media, breaking down to 6-keto $PGF_{1\alpha}$[32], in equilibrium with its lactol form (Fig. 4).

Vane and *Moncada* recently reported that prostacyclin is generated by human arterial and venous tissue from arachidonic acid *via* PGG_2 or PGH_2[2] (Fig. 4). Furthermore, they have proposed a daring homeostatic hypothesis whereby the endoperoxides serve as substrates for the generation of two labile substances with diametrically opposite biological effects.

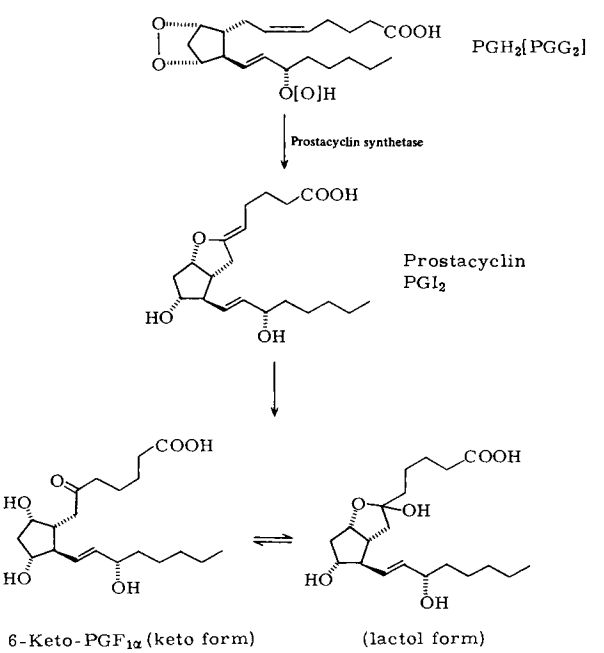


Fig. 4. Biosynthesis and degradation of prostacyclin (PGI_2, see Fig. 14).

Thromboxane A_2 generated by platelets promotes aggregation while prostacyclin produced by vascular endothelium inhibits aggregation. As corollaries they propose that 1) the basal formation of prostacyclin by vascular endothelium may be important in the maintenance of the normal integrity of vessel walls by inhibiting the adherence of platelets, 2) prostacyclin may normally limit thrombus formation, and 3) when a vessel wall is damaged, the formation of a normal hemostatic plug may be assisted by diminished prostacyclin production.

In addition to its effects on platelets, prostacyclin may play a crucial role in preventing gastric ulceration by inhibiting secretion, in blood pressure regulation by control of vascular tone, and in inflammation by inhibiting protease secretion of polymorphonuclear leucocytes. These and several other important physiological processes may be regulated by the opponent actions of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2). As in the case of cyclic AMP and cyclic GMP one could invoke a similar "ying-yang" hypothesis for the diametrically opposed effects of these two substances derived from endoperoxides.

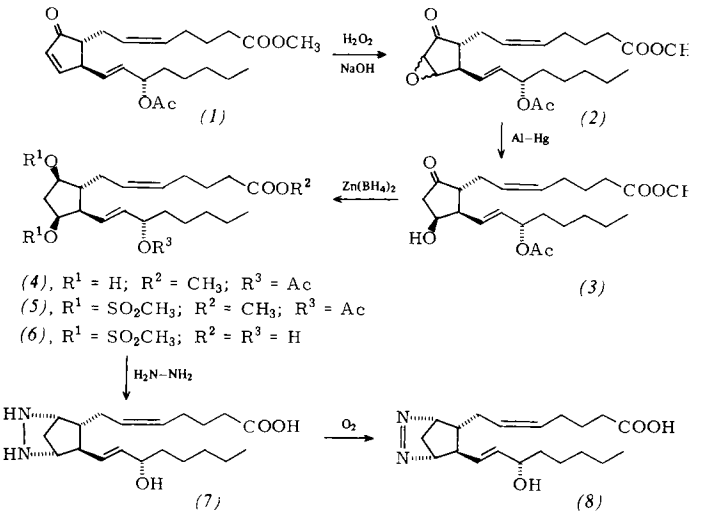


Fig. 5. Synthesis of the 6,9-azo-PGH_2 analog *(8)* from the PGA_2 derivative *(1)*.

2. Synthesis

Soon after the isolation and characterization of the prostaglandin endoperoxides H_2(PGH_2) and G_2(PGG_2) in the early 1970's[14–16] and when it was realized that these hormones were in several instances more potent than the primary prostaglandins, the design and synthesis of stable analogs of these molecules became a highly desirable goal. The synthetic chemists met this challenge with imagination successfully and rapidly, producing the first prostaglandin endoperoxide analogs in 1975. Interest in this area intensified after the isolation of thromboxanes in 1975 (*Samuelsson et al.*[22]) and prostacyclin in 1976 (*Vane et al.*[1]) and the demonstration of their remarkable biological activities. At the time that this article is being written both the prostaglandin endoperoxides H_2 and G_2 and thromboxane A_2 remain unsynthesized. The most important syntheses of prostaglandin endoperoxide analogs, thromboxane B_2 and prostacyclins reported to date are discussed below.

2.1. Prostaglandin Endoperoxide Analogs

One of the first and rather exciting developments in this area of research was the arrival of the 9,11-azo PGH_2 analog *(8)*, a highly potent and stable biological mimic of the prostaglandin endoperoxides. The first synthesis of this molecule was carried out by *Corey et al.*[33], as outlined in Fig. 5, starting from the prostaglandin A_2 derivative *(1)*, available in large quantities from the soft coral *Plexaura homoalla*[34].

The methyl ester acetate *(1)* was first converted into a mixture of the α- and β-epoxides *(2)* with basic hydrogen peroxide and then into a mixture of 11α- and 11β-hydroxy-9-oxo compounds, with aluminum amalgam, from which the β-isomer *(3)* was isolated in 29 % yield by chromatography[35]. Reduction of the 9-oxo group was effected by $Zn(BH_4)_2$ to give the diol *(4)* as the predominant product from which the dimesylate hydroxy acid *(6)* was prepared by mesylation [to *(5)*] followed by base hydrolysis. Treatment of the dimesylate *(6)* with excess hydrazine in *tert*-butanol/ethanol (3:1) under reflux for 12 h resulted in the formation of the hydrazine derivative *(7)* which was converted without isolation to the azo-PGH_2 analog *(8)* by copper(II) acetate-catalyzed air oxidation.

Widespread interest in the azo-PGH_2 analog *(8)* rapidly developed due to its high stability and remarkable potency as a biochemical mimic of the prostaglandin endoperoxides. The demand for this synthetic molecule prompted further work directed towards its synthesis, and in 1976 *Corey et al.*[36] reported a total synthesis of this molecule in its racemic form (Fig. 6). The key intermediate *(9)* was prepared from diethyl azodicarboxylate and methyl cyclopentadienecarboxylate dimers by heating in chlorobenzene at 125 °C for 50 h.

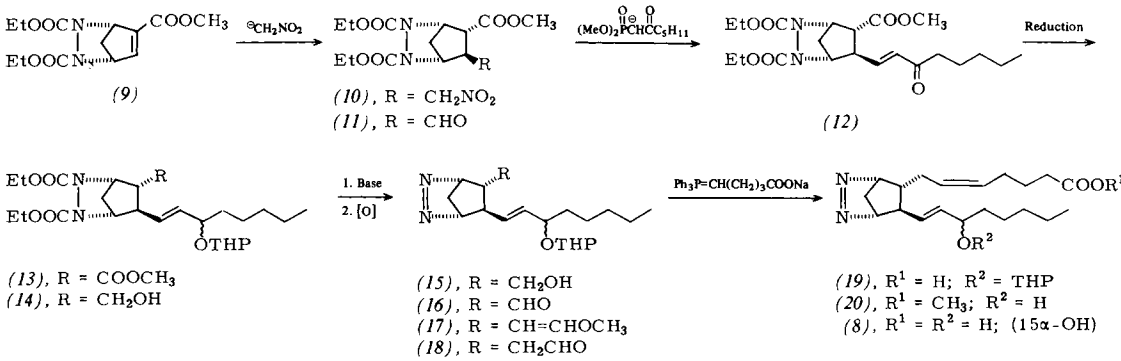


Fig. 6. Total synthesis of the 6,9-azo-PGH_2 analog *(8)*.

These conditions allow both a retro-Diels-Alder reaction of the dimers to the corresponding monomers and formation of cross adducts with the azodicarboxylate, under reversible and thermodynamic control leading to good yields of the unsaturated ester *(9)*.

Cuprate reagents failed to produce the desired products from *(9)* due to rapid β-elimination of the nitrogen bridge after the initial conjugate attack. However, conjugate addition of nitromethane was successfully carried out under carefully controlled conditions to afford the nitro compound *(10)*. The aldehyde *(11)*, obtained from *(10)* by sequential treatment with potassium hydroxide, magnesium sulfate and potassium permanganate, was converted into the enone *(12)* by the standard Emmons-Horner method and subsequently reduced with lithium selectride and protected as the tetrahydropyranyl ether *(13)* (mixture of C-15 epimers). The methyl ester *(13)* was saponified to the corresponding acid and converted to the alcohol *(14)* by $NaBH_4$ reduction of the corresponding ethyl formate mixed anhydride. Treatment of *(14)* with a strong base followed by copper(II) acetate-catalyzed air oxidation led to the azo compound *(15)*. Oxidation to the aldehyde *(16)* and subsequent condensation with methoxymethylene(triphenyl)phosphorane furnished the enol ether *(17)*. The aldehyde *(18)*, derived from *(17)* under neutral conditions [$Hg(OAc)_2$/KI] underwent the usual Wittig reaction for the attachment of the upper side chain to yield *(19)*. Esterification of *(19)* with diazomethane and removal of the tetrahydropyranyl ethers afforded the methyl esters *(20)* as a mixture of the 15α- and 15β-isomers, which could be separated chromatographically. Base hydrolysis of the 15α-alcohol led to racemic 9,11-azo-PGH_2 analog *(8)*, whereas the 15β-epimer was converted by the potassium hyperoxide/[18]-crown-6 method[37] *via* its mesylate, into the desired isomer *(8)* in high yield.

In 1975 *Bundy*[38] (Upjohn, USA) reported the stable PGH_2 analogs *(24)* and *(25)* (Fig. 7). The synthesis of *(24)* exploits an interesting, benzophenone-sensitized, photoaddition of methanol to PGA_2 *(21)*. The predominant product of this reaction[39], ketone *(22)*, was reduced selectively to the 9α-hydroxy compound with lithium perhydro-9b-boraphenalyl hydride and subsequently esterified with diazomethane and tosylated at the primary hydroxyl group to afford the tosylate *(23)*. Exposure to aqueous-methanolic potassium hydroxide led to the desired PGH_2 analog *(24)*. Synthesis of the isomer *(25)* (Fig. 7) was accomplished by conversion of the PGE_2 methyl ester *(26)* into the 9-methylene derivative *(28)* by treatment of the 11,15-bis(trimethylsilyl ether) *(27)* of *(26)* with *N*-methylphenylsulfonimidoylmethyl magnesium chloride and subsequent reductive elimination (Al—Hg) of the intermediate β-hydroxysulfoximide. Protection of the hydroxyl groups of *(28)* as triphenylsilyl ethers and selective hydroboration of the exocyclic methylene with 9-boracyclo[3.3.1]-nonane (9-BBN) resulted in the formation of the primary alcohol *(29)*, which upon mesylation and removal of the silyl groups led to the monomesylate *(30)*. Treatment of *(30)* with aqueous methanolic potassium hydroxide led to the PGH_2 analog *(25)*.

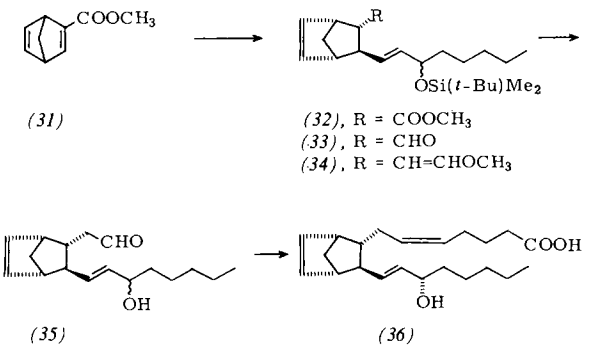


Fig. 8. Synthesis of the 9,11-etheno-PGH_2 analog *(36)*.

Later, the 9,11-etheno-PGH_2 analog *(36)* was prepared and its physiological properties investigated (Fig. 8). The first total synthesis of this stable biological mimic of prostaglandin endoperoxides was reported by *Corey et al.*[40]. These authors

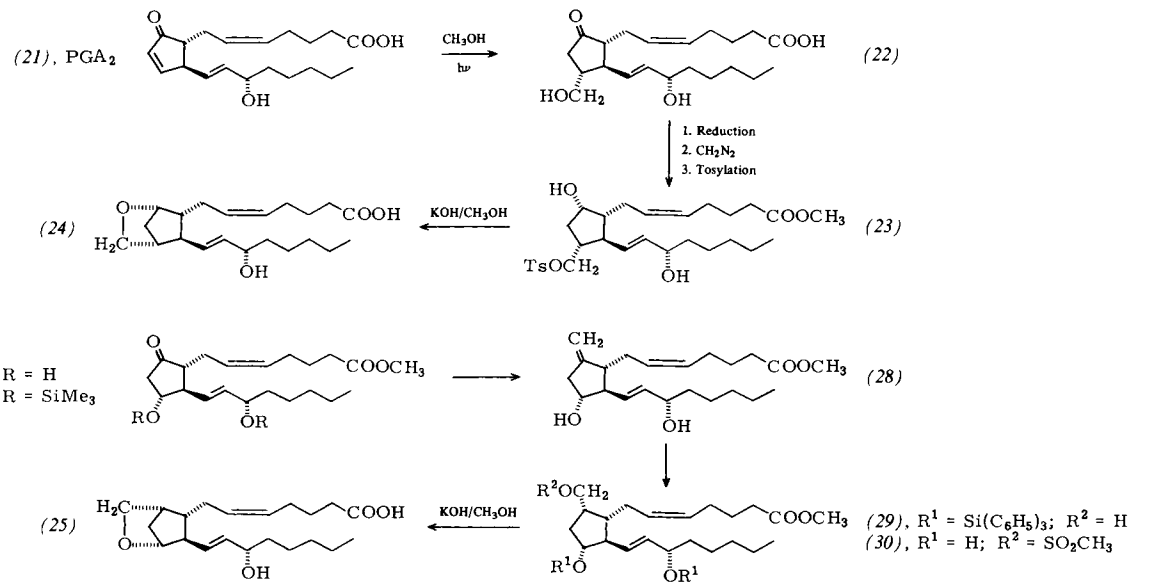


Fig. 7. Synthesis of the epoxymethano-PGH_2 analogs *(24)* and *(25)*.

started with the adduct of cyclopentadiene and methyl propiolate *(31)* which underwent conjugate addition (from the *exo* side) with the mixed cuprate reagent derived from (±)-*trans*-3-(*tert*-butyldimethylsiloxy)-1-octenyllithium and the 1-pentynylcopperhexamethyl phosphorus triamide complex to afford *(32)*. Reduction with diisobutylaluminum hydride (DIBAH) produced a mixture of the aldehyde *(33)* and the corresponding alcohol which was treated with pyridinium chlorochromate to afford pure aldehyde *(33)*. Condensation of this aldehyde with methoxymethylene(triphenyl)-phosphorane led to the enol ether *(34)*, which was converted into the hydroxyaldehyde *(35)* on acid treatment. The 15α- and 15β-epimers of *(35)* after chromatographic separation were separately converted into the PGH_2 analog *(36)* and its 15β-epimer respectively, by condensation with the sodium salt of 4-carboxybutyl(triphenyl)phosphorane. The 15β-hydroxy isomer was transformed into the 15α-hydroxy isomer by the potassium hyperoxide method[37]. Thus, esterification (CH_2N_2), conversion into the 15-mesylate and treatment with excess potassium hyperoxide in the presence of [18]crown-6 effected clean inversion of the stereochemistry at C-15 to afford the natural epimer *(36)*, making this route a completely stereocontrolled synthesis.

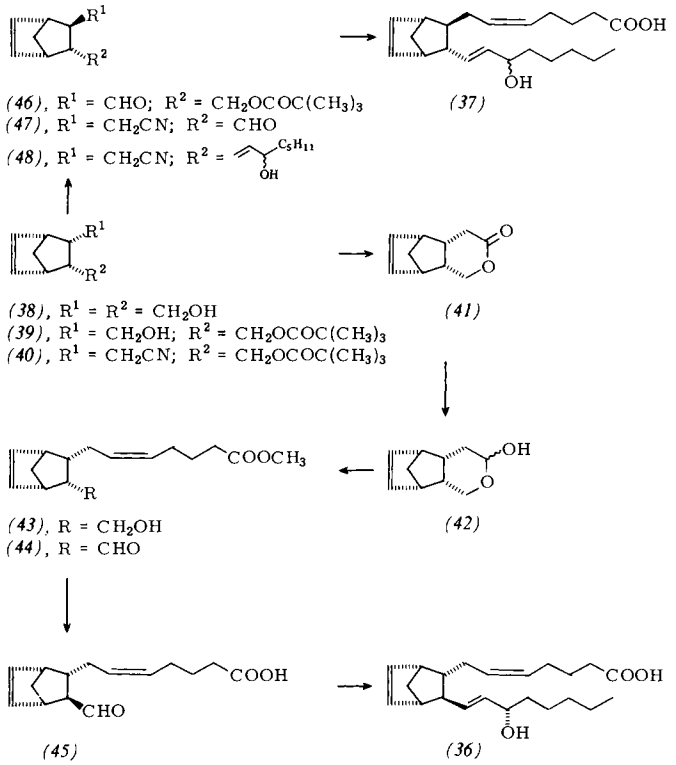
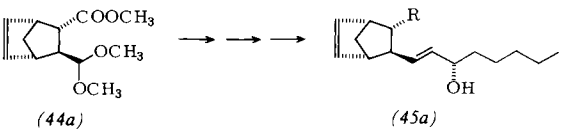


Fig. 9. Synthesis of the etheno-PGH_2 analogs *(36)* and *(37)*.

A second route to the 6,9-etheno-PGH_2 analog *(36)* was reported by a Japanese group[41], who also synthesized the 8,12-epimer *(37)*[41] starting with norbornene adducts as key intermediates (Fig. 9). The synthesis of *(36)* and *(37)* begun with the half acylation of the *cis* diol *(38)* with pivaloyl chloride to give the monoester *(39)* which was converted *via* its tosylate into the cyanoester *(40)*. Hydrolysis of *(40)* followed by treatment with hydrochloric acid afforded the lactone *(41)*, which upon reduction with DIBAH gave the lactol *(42)*. The standard Wittig reaction for attachment of the upper prostaglandin side chain[42] followed by esterification with diazomethane led to the alcohol *(43)*. This intermediate, after Collins oxidation to the aldehyde *(44)* and epimerization with pyridineacetic acid in refluxing benzene, afforded the *exo* aldehyde *(45)*. Attachment of the lower side chain by known methods[42] furnished the PGH_2 analog *(36)*.

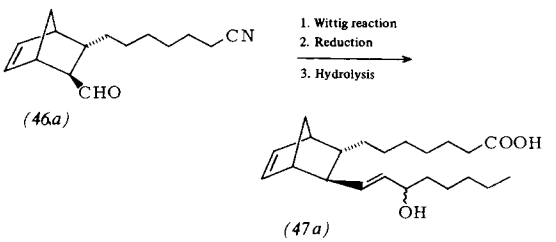
The 8,12-*epi*-etheno-PGH_2 analog *(37)* was prepared[41] by similar reactions as outlined in Figure 9. Thus, the alcohol *(39)* was oxidized with Collins reagent and the resulting aldehyde epimerized to *(46)*, which upon reduction, tosylation and cyanation followed by deprotection of the alcohol and oxidation gave the *endo* aldehyde *(47)*. Emmons-Horner condensation followed by reduction with $Zn(BH_4)_2$ led to *(48)* (mixture of diastereoisomers). Finally, reduction of the cyano group with DIBAH and reaction of the resulting aldehyde with the appropriate ylide[42] led to *(37)*, obtained as a mixture of C-15 epimers.

A series of prostaglandin endoperoxide analogs *(45a)* were synthesized and tested for biological activity by a British group[43] (ICI). The previously known bicyclo[2.2.1]heptene ester *(44a)*[44] containing the necessary functionality in the correct steric arrangement, was elaborated by the well established procedures for prostaglandin synthesis to a number of analogs *(45a)* with variations in the upper side chain (R).



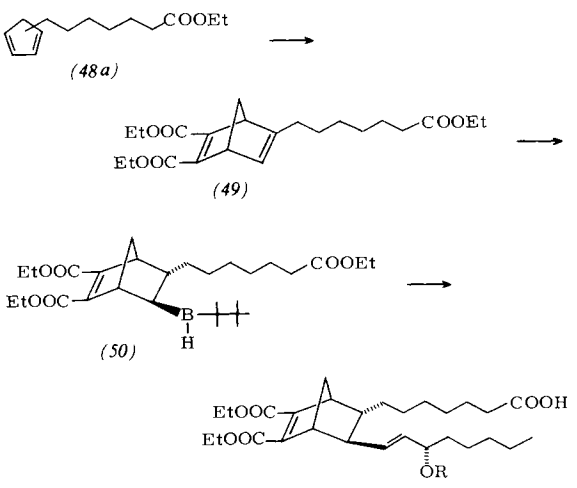
The 9,11-etheno-PGH_1 analog *(47a)* was the first prostaglandin endoperoxide analog to be synthesized. This molecule was reported as early as 1971 by *Corey et al.*[45], who carried out the synthesis of both the 15-diastereoisomers in their racemic forms from the major product *(46a)* of the Diels-Alder reaction of cyclopentadiene and *trans*-9-formyl-8-nonenenitrile. Condensation of the aldehyde *(46a)* with dimethyl 2-oxoheptylphosphonate followed by reduction of the resulting enone with $NaBH_4$ gave the expected two 15-epimeric alcohols. Base hydrolysis of the nitrile function led to the two diastereoisomers of *(47a)* in high overall yield.

The prostaglandin endoperoxide analog *(52)* has recently been described[46] although no biological data were reported. Its synthesis proceeded from the alkylated cyclopentadiene isomers *(48a)*, which underwent Diels-Alder reaction with



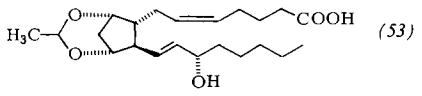
diethyl acetylenedicarboxylate to afford the bicyclo[2.2.1]heptadiene *(49)* as the predominant product. Hydroboration with thexylborane to give the presumed intermediate *(50)*, followed by sequential treatment with 3-(α-ethoxyethoxy)-1-octyne, sodium hydroxide and iodine led to *(51)* as a mixture of

isomers. Finally, removal of the ethoxyethyl group by acid treatment followed by high pressure liquid chromatography afforded pure *(52)* and its 15-epimer.



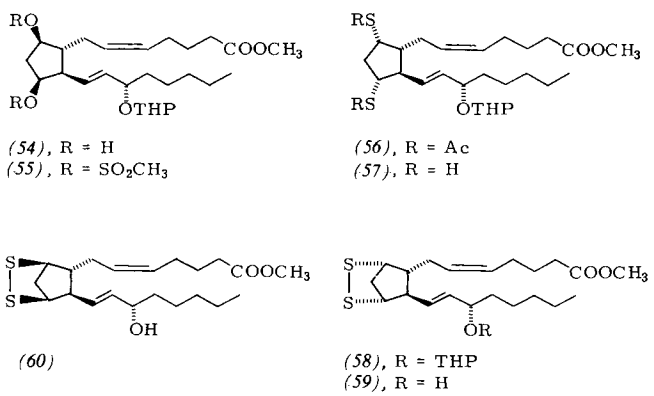
(48a) *(49)* *(50)* *(51)*, R = $CH(OEt)CH_3$ *(52)*, R = H

The same group[47] reported the synthesis and biological properties of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)-acetal *(53)* (two diastereoisomers) prepared from $PGF_{2\alpha}$ and acetaldehyde in the presence of 0.1 % HCl.



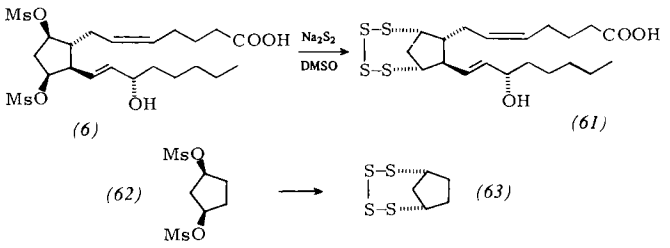
(53)

Recently the methyl ester *(59)* of the endodisulfide analog of PGH_2 and its 9,11-epimer were reported by *Hayashi et al.*[48] of the Ono company (Japan). The starting material for the synthesis of *(59)* was the 9β,11β-diol *(54)*, which was first dimesylated to give *(55)* and then reacted with excess sodium thioacetate leading to the dithioacetate *(56)*. Removal of the acetyl groups with anhydrous potassium carbonate in absolute methanol followed by oxidation of the intermediate dithiol *(57)* with manganese dioxide at low temperatures afforded the disulfide *(58)*. The methyl ester *(59)* of the disulfide PGH_2 analog was obtained after removal of the tetrahydropyranyl group by mild acid treatment. The 9β,11β-dithio analog *(60)* of PGH_2 was also synthesized starting from the 15-tetrahydropyranyl ether of $PGF_{2\alpha}$ methyl ester and following a similar sequence of reactions[48].



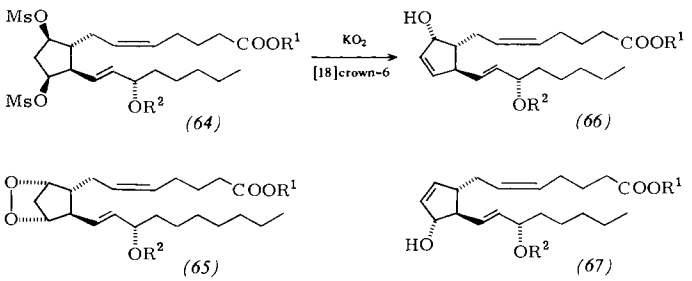
(54), R = H *(55)*, R = SO_2CH_3 *(56)*, R = Ac *(57)*, R = H *(60)* *(58)*, R = THP *(59)*, R = H

The reaction of disodium disulfide with the dimesyloxyhydroxy acid *(6)* produces smoothly, after air oxidation, the 6,9-endotetrasulfide analog *(61)*[49] of PGH_2. Interestingly enough this novel PGH_2 analog with the bulky 9,11-bridge behaves as a potent biochemical mimic[49] of the prostaglandin endoperoxides. Following the same methodology the interesting parent bicyclic system *(63)* was produced from 1,3-cyclopentylene dimesylate *(62)*[49].



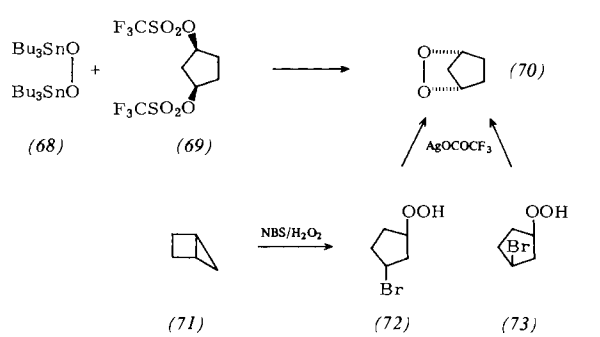
(6) *(61)* *(62)* *(63)*

To date, both prostaglandin endoperoxides H_2 and G_2 remain elusive by chemical synthesis. Attempts[50] to prepare a PGH_2 derivative such as *(65)* from the dimesylate *(64)* ($R^1 = CH_3$, H; R^2 = Ac, Si(*t*-Bu)Me_2, H) by displacement with hyperoxide failed, apparently due to the relatively drastic conditions of this method. Instead, the formation of the two isomeric allylic alcohols *(66)* and *(67)* was observed, although some endoperoxide could have been formed and not detected.



(64) *(66)* *(65)* *(67)*

Recent reports of new and milder synthetic methodology for the construction of endoperoxides are encouraging in connection with the PG endoperoxide problem. *Salomon* and *Salomon* have developed a novel method for the synthesis of dialkyl peroxides employing bis(tri-*n*-butyltin) peroxide[51] and used it to synthesize 2,3-dioxabicyclo[2.2.1]heptane *(70)*[52], the strained bicyclic peroxide nucleus of prostaglandin endoperoxides. Thus, treatment of the bis(triflate) *(69)* with bis(tri-*n*-butyltin) peroxide *(68)* under vacuum and trapping the volatile products at −78 °C, resulted in the isolation of *(70)* in 13 % yield. *Porter* and *Gilmore*[53] also developed

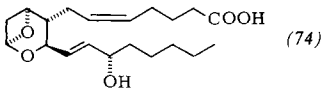


(68) *(69)* *(70)* *(71)* *(72)* *(73)*

a mild procedure that allowed them to prepare the parent bicyclic endoperoxide system *(70)* from bicyclopentane *(71)*. According to this method exposure of *(71)* to *N*-bromosuccinimide in the presence of 98% hydrogen peroxide in ether at −41 °C led to bromohydroperoxides *(72)* and *(73)* (1:1) as the major products. Treatment at the *trans* compound *(72)* with silver trifluoroacetate led quantitatively to 2,3-dioxabicyclo[2.2.1]heptane *(70)*. On similar treatment the *cis* isomer *(73)* also produced *(70)*, though at a much slower rate and in lower yield.

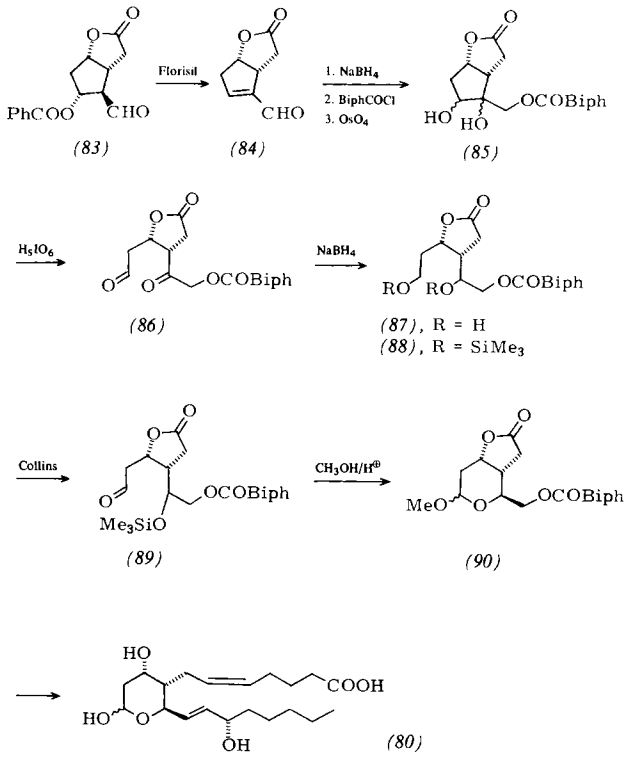
2.2. Thromboxanes

While the labile thromboxane A_2 *(74)* or any of its analogs, remain unsynthesized by chemical means, a great deal of synthetic work leading to the stable thromboxane B_2 *(80)* has already been reported. These works include partial syntheses from prostanoid precursors, total syntheses and syntheses from optically active monosaccharides.



(74)

The first thromboxane B_2 syntheses came from the Upjohn group (USA) in 1976. *Schneider* and *Morge*[54] reported an elegant and rather short route to thromboxane B_2 *(80)* from 9,15-diacetoxy-$PGF_{2\alpha}$ methyl ester *(75)*. The key step in this synthesis was a regioselective cleavage of the cyclopentane ring induced by lead tetraacetate and facilitated by the homoallyl alcohol moiety. Thus, rupture of the 11,12-bond in this fashion led to an unstable aldehyde which was protected as the dimethyl acetal *(76)* with trimethyl orthoformate and



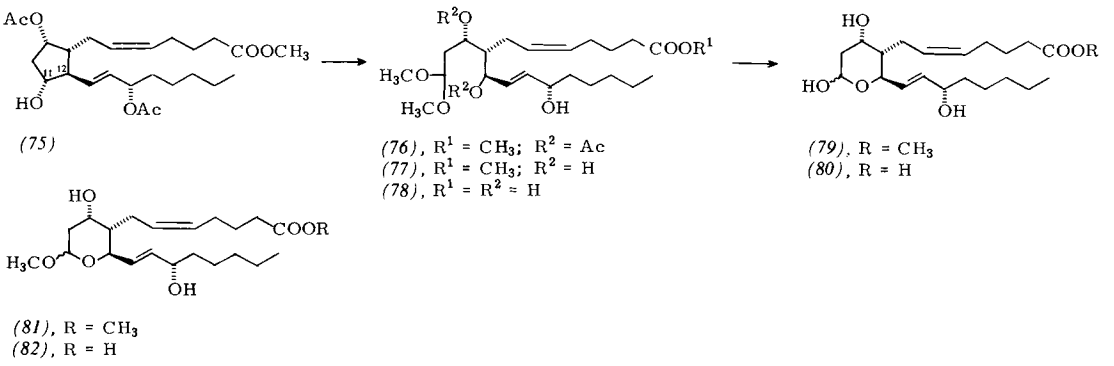
(83) *(84)* *(85)* *(86)*

(87), R = H
(88), R = $SiMe_3$

(89) *(90)* *(80)*

Fig. 10. Synthesis of thromboxane B_2 *(80)* from the bicyclic lactone *(83)*.

the 4-biphenylcarboxylate was hydroxylated with osmium tetroxide to afford *(85)*. Cleavage of this diol with paraperiodic acid led to the rather unstable aldehyde *(86)* which was reduced directly with $NaBH_4$ to afford *(87)*. Differentiation of the two hydroxyl groups of *(87)* was achieved by Collins oxidation



(75)

(76), $R^1 = CH_3$; R^2 = Ac
(77), $R^1 = CH_3$; R^2 = H
(78), $R^1 = R^2$ = H

(79), R = CH_3
(80), R = H

(81), R = CH_3
(82), R = H

pyridine hydrochloride in methanol. Removal of the acetates with methanolic sodium methoxide afforded *(77)*, whereas aqueous base gave the trihydroxy acid *(78)*. Treatment of *(77)* with acetic acid/water/tetrahydrofuran (4:2:1) led to a mixture of thromboxane B_2 methyl ester *(79)* and its cyclic methyl acetal *(81)*. Crystalline thromboxane B_2 *(80)* was obtained as the major product along with its methyl acetal *(82)* by acid hydrolysis of *(78)* employing tetrahydrofuran/water/85% phosphoric acid (12:10:1).

Starting from the prostanoid precursor *(83)*, the Upjohn group[55] developed a second route to thromboxane B_2 *(80)*. Treatment of *(83)* with florisil resulted in the formation of *(84)* which after reduction with $NaBH_4$ and protection as of its bis(trimethylsilyl ether) *(88)*, leading to the aldehyde *(89)*. Treatment of this intermediate with acid in methanol gave the acetal *(90)*, which was transformed to thromboxane B_2 *(80)* by the conventional prostaglandin methodology[42].

Yet another synthesis of thromboxane B_2 *(80)* was developed by the Upjohn group[56] starting with the prostanoid intermediate *(91)* (Fig. 11). Jone's oxidation followed by a Baeyer-Villiger reaction with *m*-chloroperbenzoic acid gave the dilactone *(92)* which on treatment with a base led to *(93)*. Reduction with diisobutylaluminum hydride (DIBAH), esterification with diazomethane and dissolution in methanol containing hydrogen chloride and trimethyl orthoformate, afforded *(94)* as the major product. Conversion of *(94)* to

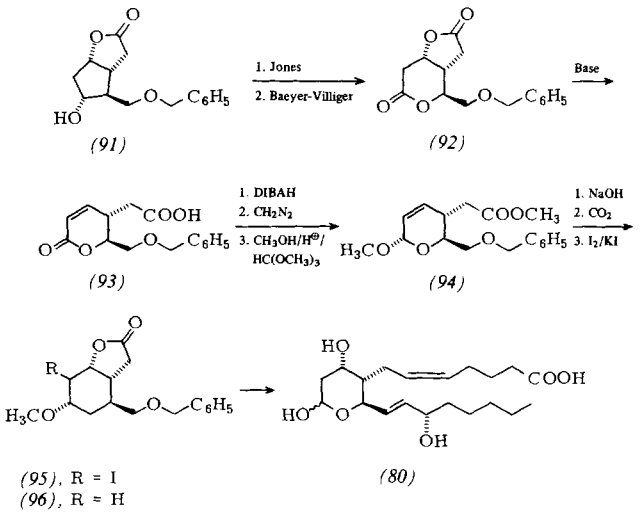
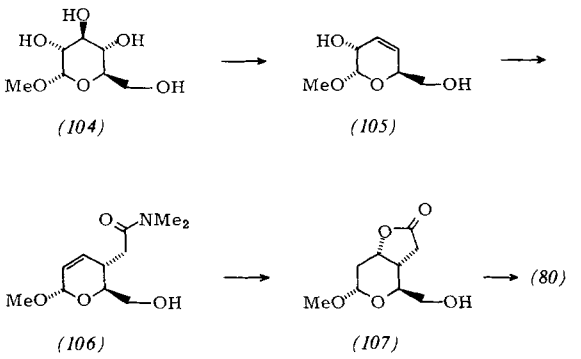


Fig. 11. Synthesis of thromboxane B_2 *(80)* from the bicyclic lactone *(91)*.

the γ-lactone *(96)* was achieved by saponification followed by iodolactonization and reductive removal of the iodine from the intermediate iodolactone *(95)* with tri-*n*-butyltin hydride. *(96)* was then converted into thromboxane B_2 *(80)* by a multistep sequence following standard prostaglandin methodology.

Canadian workers[57] have described a stereospecific total synthesis of crystalline thromboxane B_2 *(80)* from D-glucose taking advantage of the functionality and stereochemistry present in this sugar (Fig. 12).

known[59] and highly efficient sequence into the unsaturated derivative *(105)*. Claisen rearrangement of *(105)* by heating with excess *N,N*-dimethylacetamide dimethylaminal in diglyme, resulted in the stereospecific formation of the dimethylamide *(106)*. Treatment of this material with iodine readily afforded the corresponding iodolactone, which was deiodonated with tributyltin hydride leading to the hydroxylactone *(107)*, previously used as an intermediate for the synthesis of thromboxane B_2 *(80)*[54–57].



A total synthesis of (±)-thromboxane B_2 *(80)* which does not involve the intermediacy of a prostanoid precursor was developed by *Corey et al.*[60]. In this sequence, outlined in Figure 13, the enone *(108)* was alkylated with lithium isopropylamide (LDA)/allyl bromide to *(109)*, the lithium enolate

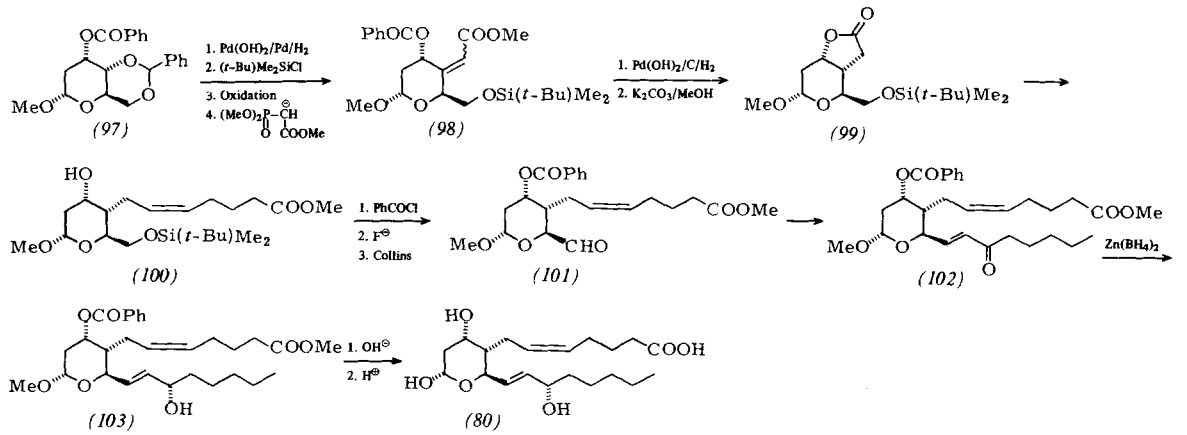


Fig. 12. Synthesis of thromboxane B_2 *(80)* from the sugar derivative *(97)*.

The derivative *(97)*, which is readily accessible from D-glucose, gave, on hydrogenolysis, selective silylation of the primary alcohol with *tert*-butyldiphenylsilyl chloride and oxidation of the secondary alcohol followed by condensation with the anion derived from trimethylphosphonoacetate and potassium *tert*-butoxide, the compound *(98)* as a mixture of geometrical isomers in high overall yield. Hydrogenation of the double bond and removal of the benzoyl groups led to the γ-lactone *(99)*. The remaining pathway followed the well known methodology of *Corey* for the attachment of the side chains.

Corey et al.[58] have also utilized sugar chemistry to produce thromboxane B_2 *(80)* by a simple and stereocontrolled route. This synthesis starts with the optically active sugar precursor α-methyl-D-glucoside *(104)*, which was converted by a of which was condensed with the aldelyde *(110)* furnishing *(111)*. Depyranylation of this intermediate led to *(112)* which, under acid conditions, cyclized to *(113)*. The protected derivative *(114)*, on reduction with $NaBH_4$, gave a diastereomeric mixture of alcohols from which the lactone *(115)* could be isolated after silver-induced removal of the thioketal function. Reduction with diisobutylaluminum hydride (DIBAH) followed by treatment with boron trifluoride in methanol led to the cyclic acetal *(116)*. Cleavage of the terminal methylene group by sequential exposure to osmium tetroxide/pyridine (to generate the diol) and sodium periodate led to the lactol *(117)*. The final steps of the synthesis involved condensation of *(117)* with the standard Wittig reagent[42] followed by exposure to 85% phosphoric acid/water/tetrahydrofuran

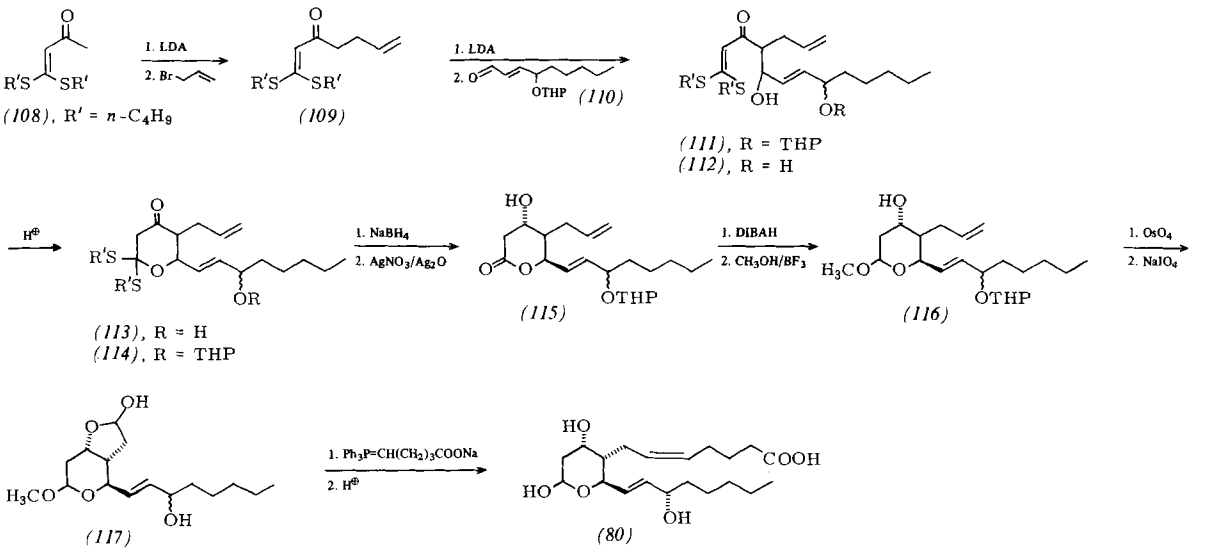


Fig. 13. Total synthesis of thromboxane B_2 *(80)* according to *Corey et al.*

(1:10:10) and chromatographic separation of thromboxane B_2 *(80)* from its 15-epimer. The 15-*epi*-thromboxane B_2 was converted into thromboxane B_2 *(80)* by (a) methyl ester-methyl acetal formation, (b) selective mesylation of the 15-hydroxyl group, (c) potassium hyperoxide/[18]crown-6 treatment to invert the C-15 configuration[37] and, (d) deprotection.

2.3. Prostacyclins

The remarkable role of prostacyclin in biological processes and its very low natural abundance dictated the need for an early chemical synthesis. *Corey* was the first to report a confirmation of the structure of prostacyclin by synthesis[31]. We have developed a simple and highly efficient synthesis[61] of this rather unstable molecule that allows its production in large quantities and in a stable form. Extensive biological investigations are now possible employing these stable basic solutions. The Upjohn group[29a] and *Hayashi*[62] have also synthesized prostacyclin and its (5*E*)-isomer. These syntheses and the syntheses of prostacyclin analogs are discussed in detail below.

The early realization that electrophilic reagents such as phenyl selenium chloride (PhSeCl) and halogens induce facile ring closure of $PGF_{2\alpha}$ derivatives to form, in high efficiency, 5-membered-ring ethers involving the C-9 oxygen and C-6, allowed us[61,63] and others[29a,31,65] to synthesize not only prostacyclin *(118)* but also a number of analogs.

Figure 14 outlines our synthesis of prostacyclin *(118)* and its isomer, (4*E*)-isoprostacyclin *(120)*. Thus, the natural form of prostaglandin $F_{2\alpha}$ methyl ester *(122)* on treatment with PhSeCl[64] in dichloromethane at −78 °C afforded the phenylselenoether *(123)* in 80% yield as a mixture of diastereoisomers. Similarly iodine reacted with *(122)* to form the iodoether *(124)* in 96% yield (mixture of diastereoisomers, in the ratio 90:6). Reaction with bromine produced a similar mixture of bromoethers *(125)*, although in lower yield. These regio- and chemospecific ring closures were expected on steric and proximity grounds. Conversion of the phenylselenoether *(123)* into the corresponding selenoxide with hydrogen peroxide followed by the expected *syn*-elimination away from the oxygen to afford a *trans* double bond, furnished the methyl ester *(121)* (95%) of (4*E*)-isoprostacyclin. Base hydrolysis of *(121)* gave (4*E*)-isoprostacyclin *(120)* in quantitative yield. Elimination of HI from either isomer of the iodoether *(124)*,

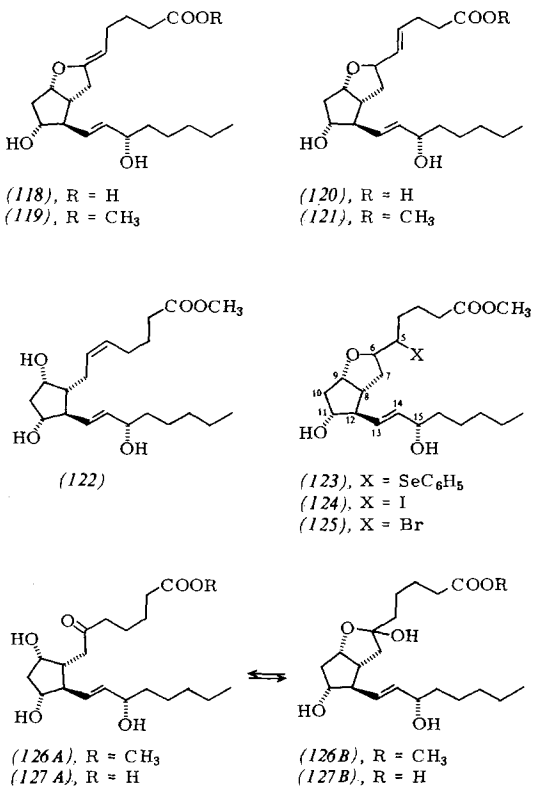


Fig. 14. Synthesis of prostacyclin *(118)* and (4*E*)-isoprostacyclin *(120)*.

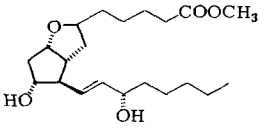
or from a mixture of the two, proceeded smoothly on exposure to sodium methoxide in anhydrous methanol at 75 °C (30 min) to afford prostacyclin methyl ester *(119)* in essentially quantitative yield. The same conversion *(124)* → *(119)* is also realized employing 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in

toluene at 110°C (30 min). The ethyl ester of prostacyclin is formed when sodium ethoxide in anhydrous ethanol is used. Use of 95% alcohol as solvent for the above reaction allows the production of prostacyclin *(118)* as its sodium salt. These basic ethanolic solutions of prostacyclin are stable at ambient temperatures for prolonged periods of time and can be directly used for bioassays.

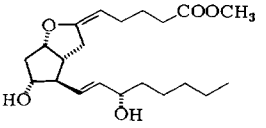
Thus the choice of the electrophilic reagent to induce the cyclization of $PGF_{2\alpha}$ methyl ester to the 5-membered ring ethers could, after elimination, lead selectively and in high overall yield to either prostacyclin *(118)* or (4*E*)-isoprostacyclin *(120)* (two C-6 epimers) by short and simple routes. Furthermore, reductive removal of the phenylseleno (PhSe—) group (or the iodide) with tri-*n*-butyltin hydride leads to the 5,6-dihydroprostacyclin methyl ester *(128)* (two C-6 epimers) in 90% yield[66].

The prostacyclin methyl ester *(119)*, although relatively stable in neutral or basic media, rearranges rapidly under acid conditions to 6-keto-$PGF_{1\alpha}$ methyl ester *(126A)*, in equilibrium with its lactol form *(126B)*. Prostacyclin *(118)* is stable in basic media but shows even higher instability under neutral or acidic conditions than its methyl ester towards formation of 6-keto-$PGF_{1\alpha}$ *(127A)*, in equilibrium with its lactol form *(127B)*. Unlike prostacyclin, (4*E*)-isoprostacyclin *(120)* is stable at ambient temperatures in both basic or acidic media.

Similar methodology has been employed by Upjohn scientists in their synthesis[29a] of prostacyclin *(118)*. Utilizing the iodoether *(124)* (Fig. 14) they have synthesized prostacyclin methyl ester *(119)* employing 1,5-diazobicyclo[4.3.0]non-5-ene (DBN) or potassium hyperoxide (KO_2) as base, and 5,6-dihydroprostacyclin methyl ester *(128)* utilizing tri-*n*-butyltin hydride to remove the iodine. Starting with 5-*trans*-$PGF_{2\alpha}$



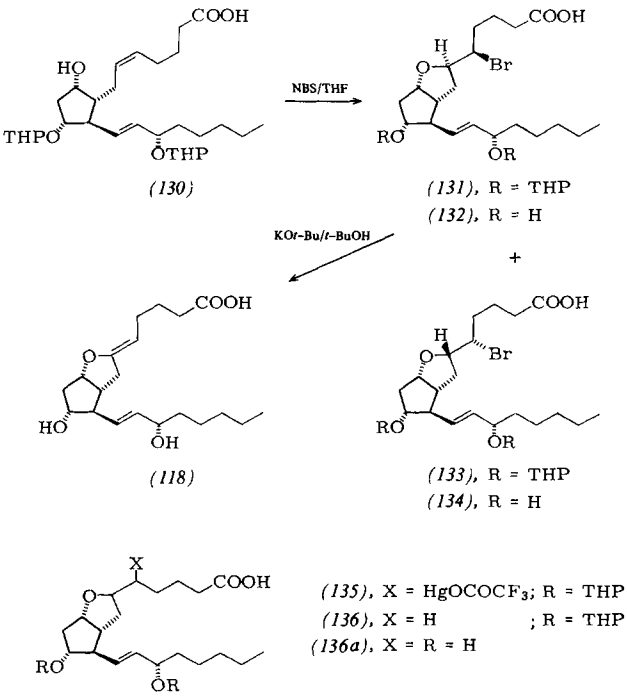
(128)



(129)

methyl ester and following the same methodology the methyl ester *(129)* of the (5*E*)-isomer of prostacyclin was synthesized[29a]. Interestingly, the (5*E*)-isomer *(129)* or the corresponding acid do not show the biological properties of prostacyclin *(118)*. *Corey*[31] and *Hayashi*[62] have also prepared the (5*E*)-isomer of prostacyclin.

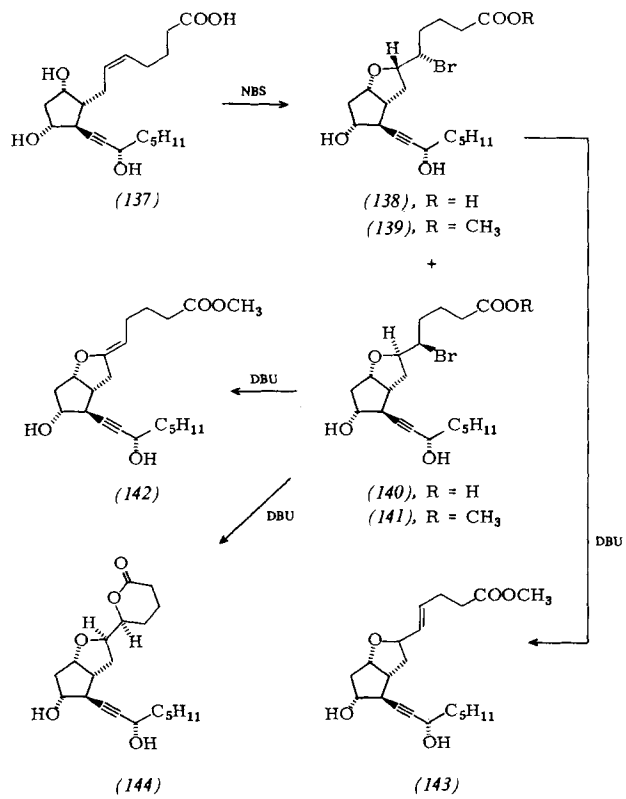
Corey's prostacyclin synthesis[31] starts with the 11,15-bis(tetrahydropyranyl) ether of $PGF_{2\alpha}$ *(130)*, which underwent bromoetherification on treatment with *N*-bromosuccinimide (NBS) in tetrahydrofuran (THF) to afford a mixture of the bromoethers *(131)* and *(133)*. This mixture was converted by mild acid treatment into the dihydroxybromoethers *(132)* and *(134)*, which were separated chromatographically (3:1 ratio). Prostacyclin *(118)* was produced from the major isomer *(132)* on exposure to potassium *tert*-butoxide in *tert*-butanol at 45°C and isolated by careful extraction at low temperatures. The bromoether *(134)* did not react under similar conditions and was recovered unchanged. Using the same starting material *(130)* and employing the selenium-based methodology[64], *Corey et al.* obtained the two isomers of (4*E*)-isoprostacyclin *(120)*[63] by the sequence (a) exposure to PhSeCl, (b) depyranylation with mild acid, and (c) oxidation with excess hydrogen peroxide[31].



(130); *(131)*, R = THP; *(132)*, R = H; *(118)*; *(133)*, R = THP; *(134)*, R = H; *(135)*, X = $HgOCOCF_3$; R = THP; *(136)*, X = H; R = THP; *(136a)*, X = R = H

The C-6 epimers *(136a)* of 5,6-dihydroprostacyclin were obtained by *Corey et al.*[31] from *(130)* by sequential treatment with mercury(II) trifluoroacetate [*(130)*→*(135)*], $NaBH_4$ [*(135)*→*(136)*] and acetic acid/tetrahydrofuran/water (3:1:1).

Recently the synthesis of 13,14-dehydroprostacyclin methyl ester *(142)* was reported by *Fried* and *Barton*[65]. Treatment of 13,14-dehydro-$PGF_{2\alpha}$ *(137)* with *N*-bromosuccinimide led



(137); *(138)*, R = H; *(139)*, R = CH_3; *(142)*; *(140)*, R = H; *(141)*, R = CH_3; *(144)*; *(143)*

to a 1:4 mixture of the cyclic bromoethers *(138)* and *(140)*. The methyl ester *(141)* of the major isomer on treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) furnished 13,14-dehydroprostacyclin methyl ester *(142)* in high yield. Similar treatment of the methyl ester *(139)* of the minor isomer was claimed to yield the (4*E*)-13,14-dehydroisoprostacyclin methyl ester *(143)*. This interesting pathway was suggested to originate from internal base abstraction of one of the C-4 hydrogens by the C-11 hydroxylate anion. The lactone *(144)* is formed from *(140)* on treatment with DBU.

We have recently synthesized several sulfur containing prostacyclins[66], and preliminary investigations indicate interesting biological properties[67] such as high potency and a higher stability than prostacyclin (cf. Addendum).

3. Biological Properties

The great enthusiasm generated in the biological sciences over the unstable prostaglandin endoperoxides, thromboxanes, and prostacyclin has quickly spread into the sector of synthetic chemistry. Several types of prostaglandin endoperoxide analogs, synthetic thromboxane B_2, synthetic prostacyclin, and various prostacyclin analogs have resulted from recent synthetic endeavors. The elegant synthetic work carried out by *Corey*'s group and other groups has produced analogs that are more stable than their natural counterparts, and in some cases more potent. With regards to the prostaglandin endoperoxides, these analogs have facilitated inquiry into the mechanism of endoperoxide-induced platelet aggregation, cardiovascular regulation by endoperoxides, the endoperoxide-induced release of renin and thyroid hormone, and the role of endoperoxides in the inflammatory process. In contrast to the prostaglandin endoperoxides, little if any investigation has probed the physiological role of thromboxane B_2, and the lack of isolated thromboxane A_2 or a stable mimic of it has hampered progress in definitively establishing the role of thromboxane A_2. Temporarily, prostacyclin has overshadowed research in this essential area. In a short span of time, several groups have synthesized this interesting molecule. Also, several more stable but less potent analogs have been synthesized, and prostacyclin has stimulated research dealing with its involvement in blood pressure regulation, shock, lysozomal stabilization, and various types of inflammation. The importance of these prostaglandins in physiology and medicine and the challenge they pose to synthetic chemistry places them in the forefront of chemical and biochemical investigation.

3.1. Naturally Occurring Prostaglandin Endoperoxides and Thromboxanes

Previous studies of the roles of prostaglandins as cellular regulatory agents have now been reexamined in light of the recent discoveries of the unstable prostaglandin intermediates. These short-lived molecules are, in some instances, hundreds of times more potent than the primary prostaglandins. Endoperoxides and thromboxanes have been implicated in such widely divergent processes as smooth muscle contraction[14], platelet aggregation[16], chemotaxis[68-71], inflammation[72], phagocytosis by polymorphonuclear leucocytes[73], the release of renin and thyroid hormone[3], and the induction of spawning in molluscs[74]. These intermediates have been detected in several types of tissues[75, 76]. All these findings have come about within the last five years.

Although the formation of an endoperoxide during prostaglandin biosynthesis was first proposed by *Samuelsson* in 1965[13], the isolation of this intermediate (PGH_2) from sheep vesicular gland homogenates took place eight years later. In the same year (1973) an additional endoperoxide (PGG_2) carrying a hydroperoxy group at the C-15 position was isolated[15, 16]. PGH_2 and PGG_2 are stable for months at $-20\,^{\circ}C$ in dry acetone, but rapidly decompose in aqueous media at $37\,^{\circ}C$. Their effects upon various *in vitro* smooth muscle preparations are considerably greater than those of PGE_2 and $PGF_{2\alpha}$.

Although the addition of arachidonic acid to platelets causes aggregation and prostaglandin formation[77], neither of the endogenously formed primary prostaglandins, PGE_2 and $PGF_{2\alpha}$, cause aggregation. Recent evidence has established that aggregation of human platelets induced by collagen, thrombin, epinephrine, and arachidonic acid is partially mediated through the production of prostaglandin endoperoxides PGG_2 and PGH_2[77, 83]. These platelet stimuli liberate arachidonic acid from the C-2 position of phospholipids by activation of phospholipase A_2[19, 84]. Therefore, the activation of the arachidonate pathway in platelets can be viewed as an amplification system for signals reaching the platelet cell surface.

Since not only endoperoxides, but also thromboxanes are formed during aggregation, either or both acting in concert may cause aggregation when the arachidonate pathway is activated[21, 78]. Thromboxane B_2 is relatively inert in terms of aggregation. At present, it is unknown whether endoperoxides must be converted into thromboxane A_2 for aggregation to occur. It is clear that thromboxane A_2 is a much more potent inducer of platelet aggregation, and inhibitor of PGE_1-stimulated cyclic AMP accumulation than PGH_2[79]. Although several agents have recently been reported as selective thromboxane synthetase inhibitors[80-82], their multiple side effects make interpretations difficult. They are used in relatively large quantities and at these concentrations they also inhibit prostacyclin synthetase. Resolution of this question may hinge upon the development of a stable biological mimic of thromboxane A_2. Although the exact arachidonate pathway intermediate responsible for aggregation is still in doubt, several aggregating agents exert their effects, in part, through the activation of this pathway.

Two products of arachidonate metabolism, namely prostaglandin endoperoxides and thromboxane A_2, also have profound effects upon vascular smooth muscle[85-87]. The endoperoxides PGG_2 and PGH_2 have been reported to contract porcine coronary and rabbit aorta[85], while they cause a transient contraction followed by relaxation in bovine coronary[27]. Recent evidence suggests that the relaxatory effects of these endoperoxides result from prostacyclin production, and that vessel preparations which do not exhibit this relaxatory activity have lost their prostacyclin synthetase activity[27]. Although thromboxane A_2 profoundly contracts all three vessels, none of the above were found to possess thromboxane A_2 synthetase activity[85]. However, human umbilical artery does contain this thromboxane synthetase activity. In addition,

thromboxane A_2 can be synthesized by circulating platelets when they are aggregated by endothelial injury. *Needleman*[85] has suggested, that coronary tone, and possibly spasm, in ischemic myocardial zones may be influenced markedly by the interplay between prostaglandins, endoperoxides, and thromboxanes formed by platelets on the one hand, and endoperoxide products (thromboxane or prostacyclin) synthesized endogeneously in the coronary arteries on the other. Likewise the modulation of vascular tone may be very important in the regulation of blood pressure.

Endoperoxides and thromboxanes may also have a pivotal role in the inflammatory processes[72]. Since the discovery that non-steroidal anti-inflammatory agents (aspirin, indomethacin) are potent inhibitors of prostaglandin synthetase[88-90] primary prostaglandins were thought to mediate the inflammatory process. However, administration of these primary prostaglandins does not fully mimic inflammation[91]. Recently, *Vane*[91] has suggested that endoperoxides and thromboxane A_2 play a major role in inflammation. Furthermore, *Kuehl et al.*[72] have demonstrated that MK-447 (2-aminomethyl-4-*tert*-butyl-6-iodophenol), which accelerates the conversion of PGG_2 into PGH_2, decreases inflammation. In focussing on this endoperoxide it is necessary to consider that PGG_2 itself may not be the active triggering agent in acute inflammation, but merely the precursor of such a substance. Thromboxane A_2 or 15-hydroperoxythromboxane A_2 may be the agents directly responsible. Alternatively, the free radical formed in the metabolism of PGG_2 and tentatively identified as a hydroxy radical[92] may be the inflammatory component liberated in the oxidation of arachidonic acid. In addition MK-447 stimulated overall primary prostaglandin synthesis in ram seminal vesicle microsomes. These observations that both inhibitors and stimulators of primary prostaglandin formation can suppress inflammation, can be interpreted as to implicate a labile prostaglandin intermediate in the inflammatory processes. Also implicated in inflammation is bradykinin, whose generation precedes or accompanies prostaglandin release in inflammatory exudates. By stimulating phospholipase A_2, bradykinin makes available arachidonic acid for prostaglandin precursors. Another interesting observation is that thromboxane B_2 promotes chemotaxis[69,70] of polymorphonuclear leucocytes, important mediators of inflammation.

Further investigation is required to elucidate the mechanism of prostaglandin endoperoxide and thromboxane action. An intriguing possibility is that they act as calcium ionophores, transporting calcium across membranes down the calcium concentration gradient. In such a manner, they could cause smooth muscle contraction and platelet aggregation. *Reed*[93] has very recently described the weak ionophore activity of endoperoxides and their analogs in transporting calcium from an aqueous phase to an organic phase and in uncoupling mitochondrial succinate oxidation.

3.2. Prostaglandin Endoperoxide Analogs

Two years prior to the isolation of the prostaglandin endoperoxides (PGH_2 and PGG_2) from sheep vesicular gland homogenates, the first endoperoxide analog was synthesized[45]. This bicyclo[2.2.1]heptene derivative *(47a)* resembles PGH_1, since it lacks the double bond between C-5 and C-6. Biologically, this PGH_1 analog proved to be a weak inhibitor of the isomerase enzyme forming PGE_1 in sheep vesicular gland microsomes[45]; however, it had no effect on the reductase catalyzing the formation of $PGF_{1\alpha}$[45]. At that time, there were several reports on the inhibition of prostaglandin formation by various unsaturated fatty acids and the synthesis of this analog did not stimulate further synthetic endeavors. In light of the minor biological activity this analog displayed, further development of PGH_2 analogs was postponed until the physiological role of prostaglandin endoperoxides was better understood.

The pace of research in this field was markedly accelerated by the discovery of the high potency of the endoperoxides in contracting smooth muscle and aggregating platelets[16]. Almost simultaneously, *Corey*[33] and *Bundy*[38], published their syntheses of the first PGH_2 analogs. Beginning with a PGA_2 skeleton, *Corey* synthesized the 9α,11α-azo-PGH_2 *(8)*, while *Bundy* produced the epoxymethano-PGH_2 analogs *(24)* and *(25)*. At once these analogs had an impact on biological research, facilitating the study of the physiological role of the prostaglandin endoperoxides. These analogs possess very nearly the same molecular geometry as PGH_2, but enjoy greater stability at pH = 7.0 and 37°C. Although there was no assurance *a priori* that these analogs would behave as mimics rather than antagonists of PGH_2, the emerging importance of the endoperoxides made the synthesis of these and other analogs highly desirable. Table 1 shows the various PG endoperoxide analogs synthesized to date.

Since the azo-PGH_2 *(8)* is the most potent and extensively studied endoperoxide analog, its biological properties will be considered in detail. Like the endoperoxides, the azo analog causes rapid and irreversible aggregation of platelets in platelet rich plasma (Fig. 15) and release of ^{14}C-serotonin from prelabeled platelets (Fig. 16). However, the azo compound was

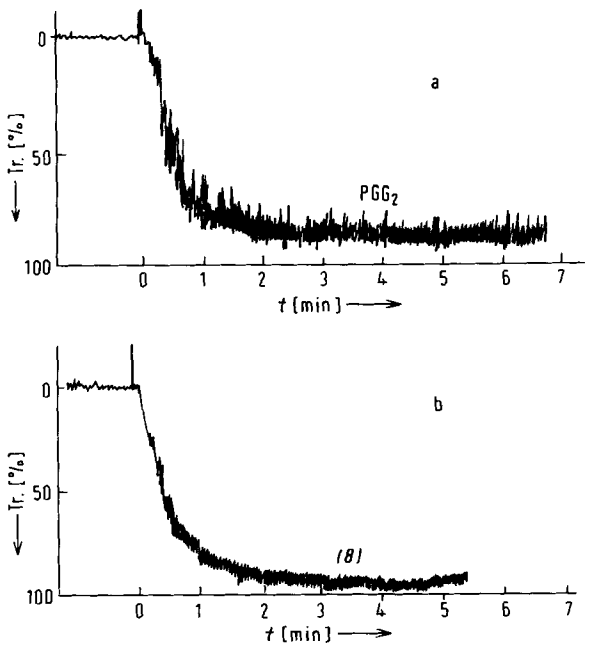
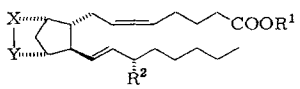


Fig. 15. Platelet aggregation in platelet rich plasma (from the same donor) induced by a) 1 μmol/l PGG_2 and b) 0.1 μmol/l azo-PGH_2. The compounds were added at zero time. Tr = light transmission.

Table 1. Prostaglandin endoperoxide analogs (cf. also *(45a)*, *(47a)* and *(60)*).



PGH_2: X—Y = O—O; R^1 = H; R^2 = OH
PGG_2: X—Y = O—O; R^1 = H; R^2 = OOH

Analog	X—Y	R^1	R^2	PGG_2-PAA [%] [a]	PGH_2-ACA [%] [b]	Ref.
(8)	N=N	H	OH	790	700	[33, 36]
(24)	O—CH_2	H	OH	63	360	[38]
(25)	CH_2—O	H	OH	370	620	[38]
(36)	CH=CH	H	OH	10	10	[40]
(52)	EtO_2C—C≡C—CO_2Et	H	OH	—	—	[46]
(53)	$OCH(CH_3)O$	H	OH	2	2	[47]
(59)	S—S	CH_3	OH	[c]	2400	[48]
(61)	S_2—S_2	H	OH	[c]		[49]
(145)	N=N	H	H			[26]
(146)	O—CH_2	H	H			[94]

[a] PAA = Platelet aggregating activity. PGG_2: 100%.
[b] ACA = Aorta contracting activity. PGH_2: 100%.
[c] Effects aggregation.

almost eight times more potent than PGG_2 in inducing aggregation (Fig. 17) and six times more active with respect to serotonin release (Fig. 16). Although both compounds cause much faster release than such aggregating agents as ADP, thrombin, and collagen, release induced by the azo compound was not as fast as PGG_2 (Fig. 16). A significant difference between PGG_2 and the azo analog (Fig. 16) as reported, is the continued release of serotonin with the azo analog as opposed to the rapid re-uptake with PGG_2. The reason proposed for this difference is the increased metabolic stability of the azo analog.

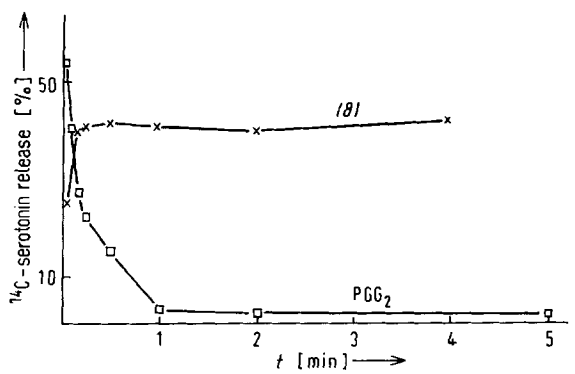


Fig. 16. ^{14}C-serotonin release from prelabeled platelets by PGG_2 (1 μg/ml) (□) and azo-PGH_2 *(8)* (0.2 μg/ml) (×).

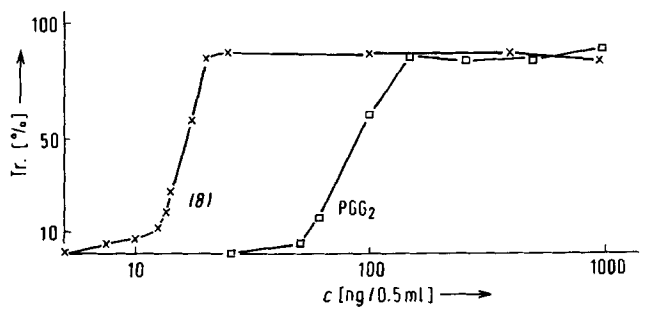


Fig. 17. Dose (log scale)-response in platelet aggregation induced with PGG_2 (□) and azo-PGH_2 *(8)* (×). Tr = light transmission.

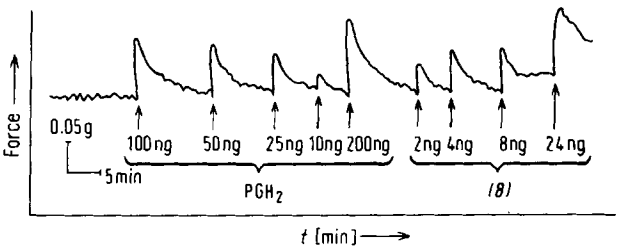


Fig. 18. Contractile effects of PGH_2 and azo-PGH_2 *(8)* on strips of rabbit aorta.

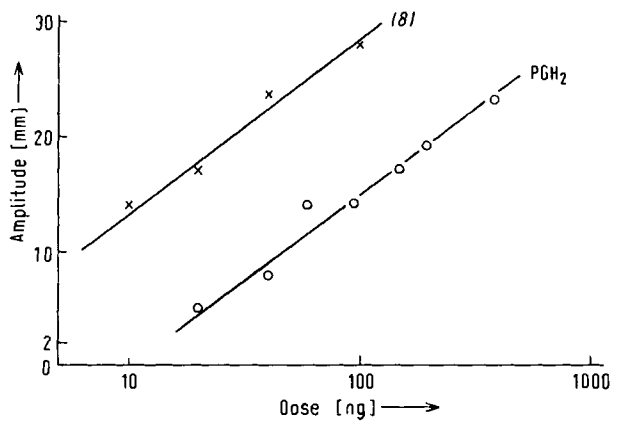


Fig. 19. Dose (log scale)-response of the contractile effect of PGH_2 (○) and azo-PGH_2 *(8)* (×) on strips of rabbit aorta.

Another system which is sensitive to the endoperoxides PGG_2 and PGH_2 as well as the azo analog *(8)*, is the rabbit aorta strip (Fig. 18). The azo analog is, however, seven times more active in contracting this smooth muscle than PGH_2 (Fig. 19) and 1500 times more potent than the primary prostaglandin $F_{2\alpha}$.

The properties of the azo analog are presently being studied with respect to release of renin and thyroid hormone. The azo analog will be of considerable value in studies related to the biological role of the unstable prostaglandin endoperoxides.

Recently, *Malmsten* has reported[94] on the biological activity of the two epoxymethano analogs *(24)* and *(25)* which also mimic the effects of the endoperoxides on platelets and rabbit aorta. The 11α,9α-epoxymethano-15-hydroxyprosta-5,13-dienoic acid *(25)* is 3.7 times more potent than PGG_2 in eliciting contractions of isolated rabbit aorta. This analog induces platelet release reaction, but is less active than the endoperoxide in this respect. Furthermore, the release of ^{14}C-serotonin induced by this analog is inhibited by indomethacin, indicating that endogenous endoperoxide production is required. Interestingly the corresponding 9α,11α-isomer *(24)* was less active than PGG_2 in the test system employed[94].

Several other analogs of PGH_2 (Table 1) have been synthesized and in some cases their biological properties have been determined. For instance, even the bulky acetal endoperoxide analog *(53)* has some activity in aggregating platelets and contracting smooth muscle[47]. The utility of such analogs will become more apparent when the endoperoxide receptor is studied.

The endodisulfide analog of PGH_2 *(59)*[48] is also of special interest, since a dithio linkage is chemically more stable than a peroxide moiety and the molecular geometry of this structure approximates that of PGH_2. This cyclic disulfide *(59)* is reported[48] to be 24 times more potent than PGH_2 in contracting aorta strips, making it the most active smooth muscle contracting analog. Rapid and irreversible aggregation occurs when this disulfide analog is added to washed platelets[48]. Even more interesting is the finding that platelet aggregation occurs when the endotetrasulfide PGH_2 analog *(61)*[49] is added to platelet rich plasma, indicating that the bulky sulfur groups are accommodated by the endoperoxide receptor.

The azo- and epoxymethano-15-deoxy-PGH_2 analogs *(145)* and *(146)*, lacking the oxygen at the C-15 position, were reported[26, 95] to possess significant thromboxane synthetase inhibiting activity although they also inhibit prostacyclin synthesis to some extent.

3.3. Prostacyclin

The discovery late in 1976[1] of a novel prostaglandin which was found to be the most potent inhibitor of platelet aggregation known has not only revolutionized current concepts in thrombosis and hemostasis but has also intensified the pace in one of science's fastest developing fields. This discovery came only one year after the finding that thromboxane A_2 was an extremely effective vasoconstrictor and platelet aggregator, two properties which promote thrombus formation[22]. Since this new prostaglandin, named prostacyclin (PGI_2 *(118)*), has diametrically opposite effects, *Moncada* and *Vane* have proposed that a balance between the activities of these prostaglandins determines thrombosis and hemostasis[25, 27, 28]. Taking into consideration only prostacyclin's vasodilatory and anti-aggregating properties, this local hormone has already earned a position of foremost importance in medicine.

Each year stroke and heart attack claim thousands of lives, and the formation of small clots and thrombi in circulation is a major contributing factor to these deaths. In addition, endothelial injury appears to be a prerequisite for thrombus formation. *Moncada* and *Vane*[2] have shown that prostacyclin is synthesized by human arteries and veins and the enzyme that generates PGI_2 is located in the endothelium, the innermost lining of blood vessels. These investigators suggest that basal prostacyclin formation may be important in maintaining the normal integrity of endothelium by inhibiting platelet adhesion, and that prostacyclin may normally limit thrombus formation. Recent evidence by *Minick et al.*[96] indicates that lipid accumulation is greatest beneath damaged endothelium which is regenerating. This lipid accumulation constitutes one of the initial phases of atherosclerotic plaque formation. Since *Moncada* and *Vane*[27, 28] have demonstrated that lipid hydroperoxides (*e.g.* 15-hydroperoxyarachidonic acid) effectively inhibit prostacyclin synthetase, the presence of these hydroperoxides in atherosclerotic plaques might explain the increased incidences of thrombosis in atherosclerotic patients. Therefore, endothelial injury is necessary for both thrombus and plaque formation, two processes which are central to cardiovascular disease.

Platelets have also been implicated as instrumental agents in the blockage of coronary and cerebral arteries. A growth factor released from platelets as well as low density lipoprotein will lead to increased proliferation of vascular smooth muscle cells and fibromuscular intimal thickening[97–99]. Such thickening will decrease the internal vessel diameter. Stroke or heart attack will occur when such a diseased vessel is contracted by thromboxane A_2 or occluded by a thrombus. Prostacyclin would prevent both events by inhibiting thrombus formation and dilating smooth muscle. Further investigation is required to determine if PGI_2 would also inhibit release of platelet growth factor.

Although the majority of investigations with prostacyclin have been carried out *in vitro*, investigators are beginning to explore the effects of PGI_2 *in vivo*. *P. W. Ramwell*[105] and *A. M. Lefer*[101] have found that systemic infusion of PGI_2 markedly reduces blood pressure in cats, dogs, and rhesus monkeys. The proposed mechanism for this action is a vasodilatory induced decrease in resistance to blood flow of the systemic circulatory system. Prostacyclin may also be useful in the treatment of several types of shock. For example, in hemorrhagic shock, vasoconstriction may severely limit the flow of blood to the gut and kidneys. Replacement of the blood volume lost will easily redilate the gut vessels but flow through the kidney may be impeded for a long period of time. During this interval the kidneys may infarct. In addition, prolonged vasoconstriction in the gut region may release proteases from liver and pancreatic lysozomes. Prostacyclin may attenuate these deliterious effects by maintaining a small amount of blood flow through these areas.

Despite the large amount of physiological work with prostacyclin, relatively little has been done to determine its mode of action. Recently, prostacyclin has been shown to elevate cyclic AMP concentrations in human platelets[102, 103]. This elevation of cyclic AMP inhibits hydrolysis of arachidonic acid from platelet phospholipids, and prevents the production of endoperoxides[104]. Whether inhibition of aggregation is also due to cyclic AMP elevation still remains to be determined.

3.4. Prostacyclin Analogs

In light of the physiological importance of prostacyclin *(118)* and its unstable nature, the design of stable prostacyclin

mimics merits high priority. Up to date, a number of analogs have been reported[31,63,65]: 5,6α- and 5,6β-dihydroprostacyclin [cf. *(128)*]; (4*E*)- and 6-epi(4*E*)-isoprostacyclin [cf. *(120)*]; 13,14-dehydroprostacyclin methyl ester *(142)*. Only the last of these, which closely resembles PGI_2, possesses activity comparable to prostacyclin[65]. All the other analogs are several times less potent than the natural product[105]. Recently, we have synthesized a sulfur analog of prostacyclin[66] which has divergent activities. Its potency in inhibiting platelet aggregation is between two to four times less than the natural product[67]. However, thiaprostacyclin is considerably more stable at neutral pH. In contrast to the vasodilatory effects of prostacyclin, the sulfur-analog is a potent constrictor of isolated cat coronary artery[67]. In this regard, it mimics the endoperoxides (PGG_2 and PGH_2) and thromboxane A_2.

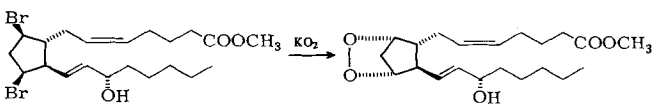
4. Conclusion

Without a doubt, prostaglandin research is one of the most exciting and fastest developing areas in synthetic chemistry, biochemistry, physiology, and medicine. Since the beginning of the prostaglandin era these local hormones have had great potential as therapeutic agents. Today, a number of synthetic prostaglandins are already in use in human and veterinary medicine and many more are currently under clinical investigation. The discovery of the very active unstable prostaglandin endoperoxides, thromboxanes, and most recently, prostacyclin, has significantly augmented interest in them. The optimists are more excited than ever that these developments will lead to the long-sought specific pharmacological agents for the treatment of a wide spectrum of diseases.

It is greatly hoped that this article has gathered together useful information for chemists, biochemists, physiologists, and pharmacologists and that these scientists will use this information as a platform from which they will view the future challenges with excitement and imagination.

5. Addendum

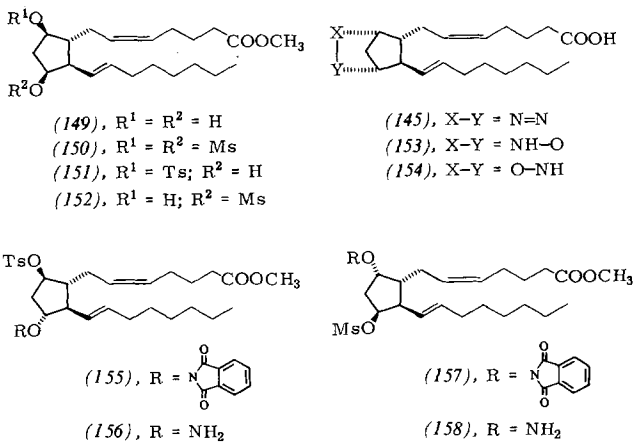
Since the preparation of the original manuscript, a number of significant developments in this area have been reported. This addendum contains some of these results concentrating on the chemistry and is intended to bring the present article up to date at the time of the 1978 Winter Prostaglandin Conference (January, 1978, Sarasota, Florida, USA).



(147) *(148)*

PGH_2 methyl ester *(148)* has been synthesized chemically for the first time by *Johnson et al.*[106] of the Upjohn Company from the dibromide *(147)*. This precursor was obtained from $PGF_{2\alpha}$ methyl ester by a multistep sequence and reacted with potassium hyperoxide in dimethylsulfoxide (DMSO)[37] in the presence of [18]crown-6[37] under carefully controlled conditions to afford the PGH_2 derivative *(148)* in very low yield. Studies on the thermal decomposition of 2,3-dioxabicyclo-[2.2.1]heptane *(70)* have been published[107].

A number of 15-deoxy-PGH_2 analogs with interesting properties have been synthesized. The 9,11-azoprosta-5,13-dienoic acid (15-deoxyazo-PGH_2) *(145)* was prepared (cf. Table 1)[108] from the dimesylate *(150)* following similar methodology to that used in the synthesis of the azo-PGH_2 analog *(8)*[33]. The requisite 9β,11β-dimesylate *(150)* was obtained from $PGF_{2\alpha}$ in a number of steps that included hydrogenolysis of the 15-hydroxy group (Li/neopentyl alcohol/$MeNH_2$) and inversion of the 9- and 11-hydroxy groups (benzoic acid/triphenylphosphine/diethyl azodicarboxylate). The two isomeric 15-deoxy-PGH_2 analogs *(153)* (11,9-epoxyimino) and *(154)* (9,11-epoxyimino) were synthesized[109] from the ester *(149)* as follows: Taking advantage of the different steric environment of the two hydroxy groups, the tosylate *(151)* and the mesylate *(152)* were first prepared. Exposure of *(151)* to triphenylphosphane, *N*-hydroxyphthalimide and diethyl azodicarboxylate afforded the precursor *(155)*. When *(155)* was treated with hydrazine the hydroxylamine derivative *(156)* was formed and cyclized spontaneously to *(153)*, after ester hydrolysis. In a similar manner, *(154)* was obtained from the mesylate *(152)* *via* the intermediates *(157)* and



(149), $R^1 = R^2 = H$
(150), $R^1 = R^2 = Ms$
(151), $R^1 = Ts$; $R^2 = H$
(152), $R^1 = H$; $R^2 = Ms$

(145), X–Y = N=N
(153), X–Y = NH–O
(154), X–Y = O–NH

(155), R = N-phthalimido
(156), $R = NH_2$

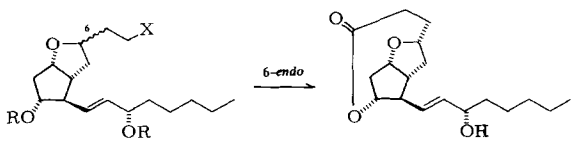
(157), R = N-phthalimido
(158), $R = NH_2$

(158). All three 15-deoxy-PGH_2 analogs *(145)*, *(153)* and *(154)* were stable and showed inhibitory activity towards human platelet thromboxane A_2 synthetase, the most specific one being the 11,9-epoxyimino-PGH_2 analog *(153)*. Since these analogs antagonized the human platelet aggregation induced by endoperoxide PGH_2 or aracidonic acid, the important conclusion that PGH_2 must be converted to thromboxane A_2 in order to induce platelet aggregation was drawn[108].

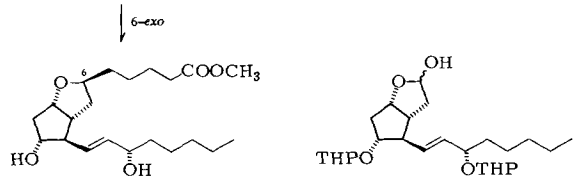
An intense effort in the prostacyclin area in the last few months resulted in the synthesis of a plethora of interesting analogs.

Nelson[110] provided the first chemical proof of the stereochemistry at C-6 of PGI_1 isomers and formulated a useful empirical "rule" for the assignment of the C-6 configuration of PGI_1 analogs. By a series of steps lactol *(163)* was converted into the two 6-epimeric acids *(160a)* and *(160b)* which were separately subjected to the "double activation" lactonization procedure (dipyridyl disulfide/triphenylphosphane)[111]. Only one acid, the *endo* isomer *(160b)* cyclized to give the lactone *(162)*. The more abundant 6-*exo* isomer *(160a)* was converted into the PGI_1 derivative *(128)* (*via* aldehyde *(161)*) and compared to the PGI_1 isomers previously obtained from a $PGF_{2\alpha}$

precursor[29a]. Thus it was established and generalized that the PGI_1 analogs with the 6-*exo* configuration exhibit an ill-defined quartet centered at about $\delta = 4.4$–4.5 ($J = 6$ Hz) in their ^{1}H-NMR spectra ($CDCl_3$) and are slower moving on silica gel than the corresponding *endo* isomers.

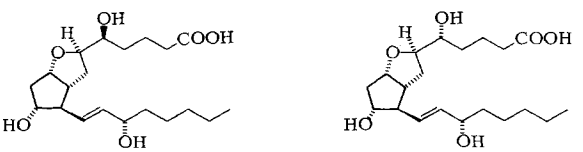


(159a),(159b), X = Ts; R = THP
(160a),(160b), X = COOH; R = H
(161), X = CHO; R = H

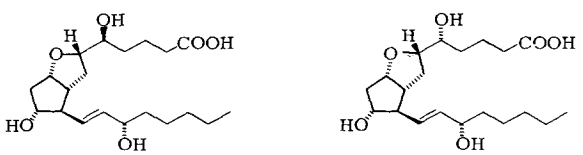


(128) *(163)*

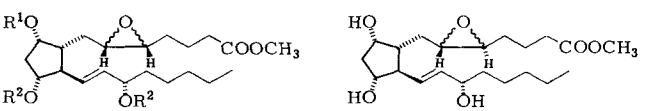
All four possible isomers of 5-hydroxy-PGI_1 [*(164)*—*(167)*] were synthesized. *Sih et al.*[112] prepared the (5*R*,6*R*)- and the (5*S*,6*S*)-isomers *(165)* and *(166)* from the epoxide *(168)*, $R^1 = H$, $R^2 = Si(t\text{-}Bu)Me_2$, by silica gel-promoted cyclic ether formation accompanied by epoxide opening. No PGI_2 was detected when 9-tritiated *(165)* or *(166)* was incubated with dog aortic microsomes suggesting that these 5-hydroxy-PGI_1 analogs are not biosynthetic intermediates in the enzymatic formation of PGI_2 from the endoperoxides PGH_2 or PGG_2.



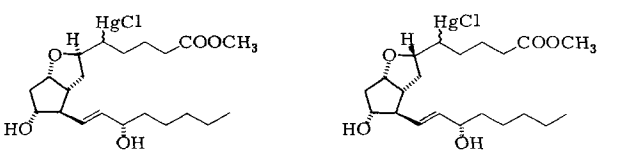
(164), (5*S*, 6*R*) *(165)*, (5*R*, 6*R*)



(166), (5*S*, 6*S*) *(167)*, (5*R*, 6*S*)



(168) *(169)*

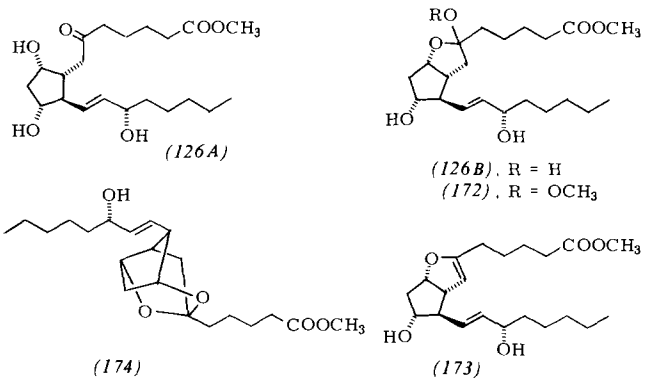


(170a), *(170b)* *(171a)*, *(171b)*

Johnson et al.[113] synthesized the PGI_1 analogs *(164)* and *(167)* in addition to *(165)* and *(166)* by two different methods.

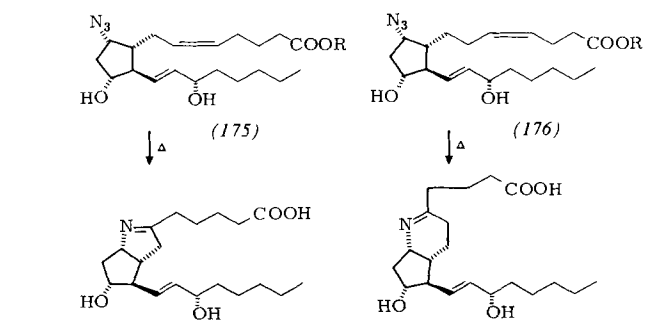
In the first route the *cis*-epoxide *(168)*, $R_1 = R_2 = H$, was utilized to obtain *(165)* and *(166)* and the *trans* epoxide *(169)* to obtain isomers *(164)* and *(167)* by similar methodology to that used by *Sih*[112] (silica gel, ester hydrolysis). In the second route $PGF_{2\alpha}$ methyl ester was treated with mercury(II) acetate followed by sodium chloride to give four diastereomeric cyclic ethers separated into two pairs *(170a)/(170b)* and *(171a)/(171b)*. Sodium borohydride in the presence of oxygen converted *(170a)/(170b)* into *(164)* and *(165)* and *(171a)/(171b)* into *(166)* and *(167)*, respectively.

Hayashi et al.[114] recently synthesized two novel isomeric forms of prostacyclin (PGI_2) from 6-oxo-$PGF_{1\alpha}$ *(126A)* $\rightleftharpoons$ *(126B)*. The PGI_2 isomer *(174)* which represents an internally protected form of *(126)* was obtained from *(126)* by stirring with powdered molecular sieves 4A and kiesel gel in dichloromethane. We have also synthesized this compound *(174)* from PGI_2 methyl ester *(119)* and *p*-toluenesulfonic acid in dry benzene at 25°C (80%). The Δ^6-PGI_2 isomer *(173)* was obtained by pyrolysis of the methoxy compound *(172)* (obtained from *(126)* and methanol under acid conditions) in hexamethylphosphoric triamide at 180°C. An alternative procedure[114] for the preparation of *(173)* from *(126)* involved (a) complete trimethylsilation, (b) GC isolation of the major component (260°C), and (c) deprotection of the 11- and 15-hydroxy groups (K_2CO_3/methanol). The internal ketal *(174)* was found to be biologically inactive, whereas the Δ^6-prostacyclin isomer *(173)* showed potent activity (11.7 times as active as PGE_1) as an inhibitor of rat platelet aggregation[114].



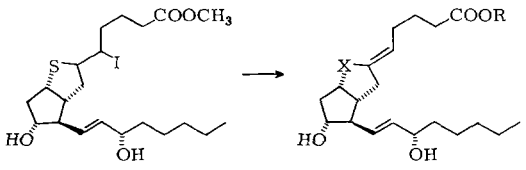
(126A) *(126B)*, R = H
(172), R = OCH_3
(174) *(173)*

Upjohn scientists have recently reported the nitrogen-containing prostacyclin analogs *(177)* and *(178)*[115] which



(175) *(176)*
(177) *(178)*

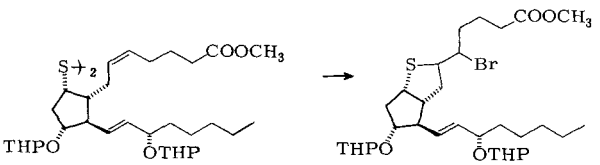
showed both high stability and potency in inhibiting platelet aggregation. The synthesis of *(177)* proceeded smoothly from the $PGF_{2\alpha}$-azido derivative *(175)* by an interesting thermolytic process accompanied by the loss of nitrogen. The six-membered ring PGI_2 analog *(178)* was obtained in an analogous manner by thermolysis of *(176)*[115].



(179)

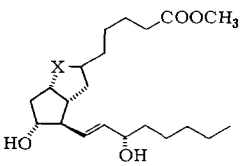
(180), X = S
(181a), *(181b)*, X = SO
(182), X = SO_2

A series of sulfur-containing prostacyclins have been synthesized[116–120]. The thiaprostacyclin *(180)*, R = H[119], a stable and biologically potent analog of PGI_2 having a sulfur-containing ring, was prepared from the cyclic iodothioether *(179)* by base (DBU) elimination followed by ester hydrolysis. The iodide *(179)* was obtained from the thiol *(188)*[119] upon addition of iodine at low temperatures. The desired (5*Z*) geometry in *(180)* was secured by intramolecular *trans* addition to the *cis* double bond of *(188)* followed by *trans* E_2-type elimination of hydrogen iodide from *(179)*. Japanese workers



(183) *(184)*

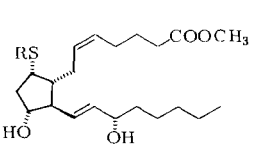
have also prepared the thiaprostacyclin *(180)*[116,117]. *Shibasaki* and *Ikegami*[116] arrived at *(180)* in an elegant manner *via* the bromide *(184)* which was obtained from the disulfide *(183)* and bromine.



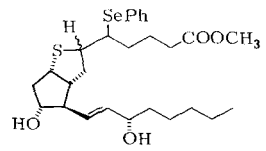
(185), X = S
(186a), *(186b)*, X = SO
(187), X = SO_2

The 5,6-dihydrothiaprostacyclin *(185)* has also been prepared[118] by acid treatment of the thiols *(188)* or *(195)*. Controlled oxidation of *(185)* afforded selectively *(186a)*/*(186b)* (two sulfoxide isomers) or *(187)*[118]. Similar acid-catalyzed cyclizations have also been reported by *Shibasaki* and *Ikegami*[116].

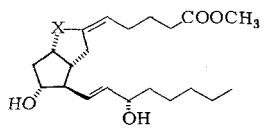
Selenium-induced ring closure of *(188)* or its acetate *(189)* led to the phenylselenothioether *(190a)* which upon oxidation followed by *syn*-elimination resulted in the formation of a number of (5*E*)-PGI_2 analogs[120]. Thus, oxidation of *(190a)* with 2.2 equivalents of *m*-chloroperbenzoic acid (78→25 °C) led selectively to a mixture of two sulfoxide isomers, (5*E*)-thiaprostacyclin methyl ester *S*-oxides *(191a)*/*(191b)*, which were separated chromatographically, *(191a)* being the major product. With 2.2 equivalents of *m*-chloroperbenzoic acid (−78→25 °C) and excess hydrogen peroxide (25 °C) the (5*E*)-thiaisoprostacyclin methyl ester *S*,*S*-dioxide *(192)* was formed selectively and in high yield. The (4*E*)-*S*,*S*-dioxide *(193a)* was obtained with its conjugated isomer *(192)* upon oxidation of *(190a)* with excess hydrogen peroxide.



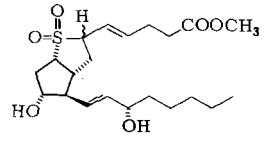
(188), R = H
(189), R = Ac



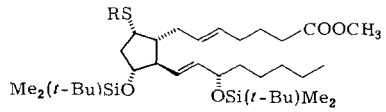
(190a), *(190b)*



(191a), *(191b)*, X = SO
(192), X = SO_2

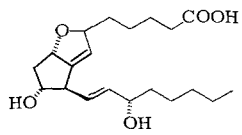


(193a), *(193b)*

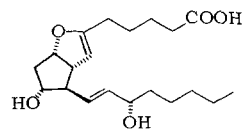


(194), R = Ac
(195), R = H

Utilizing similar methodology and starting with the 9-acetylthio-5-*trans*-$PGF_{2\alpha}$ derivative *(194)*[118], the cyclic sulfoxides *(181a)* and *(181b)*[120], the cyclic sulfones *(182)*[120] and *(193b)* [6-epimer of *(193a)*][120] were synthesized; *(181a)*, *(181b)* and *(182)* have the same natural (5*Z*) geometry.



(196)



(197)

These stable sulfur-containing prostacyclins show interesting and divergent biological properties. Thus, thiaprostacyclin *(180)*, for example, showed comparable potency to natural prostacyclin in inhibiting platelet aggregation and potent vasoconstricting activity in isolated cat coronary artery, while the sulfones *(182)* and *(193a)* showed antagonistic action against PGI_2 in inhibition of platelet aggregation.

The novel structure *(196)* assigned by *Pace-Asciak* and *Wolfe*[29] to a major prostaglandin biosynthesized from arachidonic acid by rat stomach homogenates has recently been revised to structure *(197)* by *Sih* and *Huang*[121], mainly on the basis of mass spectroscopic evidence [cf. *(173)*].

Several important biological studies involving prostacyclin (PGI_2) have been carried out. The cardiovascular properties of PGI_2 have been studied by *Lefer et al.*[101] by infusing PGI_2 into anesthetized cats. As shown in Figure 20, PGI_2 reduces significantly both the mean arterial blood pressure and the total peripheral resistance without affecting the heart rate. *Vane* has recently reported[122] that PGI_2 infused into anesthetized dogs on kidney machines prevented both platelet loss and microthrombi formation. *Fried*'s compound, 13,14-didehydroprostacyclin methyl ester *(143)* was found to exhibit

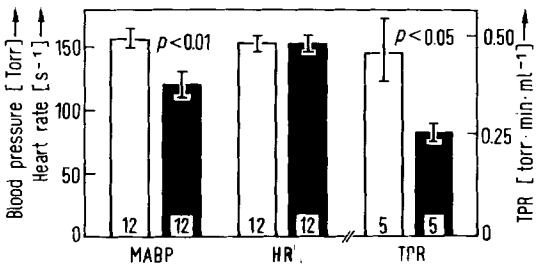


Fig. 20. Hemodynamic response in cats 10 minutes after PGI_2 infusion (2.7×10^{-9} mol·kg^{-1}·min^{-1}, *i.v.*). Open bar heights indicate pre-infusion mean values (control). Solid bars indicate mean values attained 10 minutes after infusion. Numbers within bars indicate the number of cats in which responses were measured. Left two bars represent values of mean arterial blood pressure (MABP) measured by intra-aortic catheters positioned *via* the right common carotid artery. PGI_2 infusion resulted in significantly reduced MABP ($p<0.01$) at 10 minutes compared to pre-infusion control MABP. Middle two bars indicate the heart rate (HR) response to PGI_2 infusion. No significant changes from pre-infusion HR was observed after 10 minutes of PGI_2 infusion. Right two bars represent values for total peripheral resistance (TPR). PGI_2 infusion resulted in significant reduction in TPR ($p<0.05$).

unusual pulmonary vasodilatory activity[1 2 3]. These and other novel biological properties of prostacyclins strongly suggest possible therapeutic uses of these substances.

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Skeletal Rearrangements of Organoalkali Metal Compounds

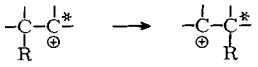
By Erling Grovenstein, Jr.[*]

Dedicated to Professor Avery A. Morton on the occasion of his 85th birthday

Organometallic compounds of the alkali metals undergo concerted [1,*n*] sigmatropic migration of aryl, vinyl, carbonyl, alkoxycarbonyl, silyl, germyl, and related groups. Sigmatropic migration of alkyl, benzyl, and hydrogen occur only under special circumstances and then may occur by an alternate fragmentation-recombination pathway. Allyl groups may migrate by the latter process or by a concerted [2,3] sigmatropic reaction. These molecular rearrangements are discussed from the viewpoint of simple molecular orbital theory. By suitable choice of the alkali metal, temperature, ligands of the alkali cation and/or the solvent, considerable control may be exercised over the rate of rearrangement, the relative migratory aptitude of groups, and the mechanistic pathway.

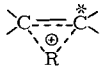
1. Introduction

Early progress in the elucidation of the structures of organic compounds was made possible by the general correctness of the *principle of minimum structural change*[1] or of the *non-occurrence of molecular rearrangements* during organic reactions. Nevertheless, *Fittig*'s discovery[2] of the transformation of pinacol into pinacalone by treatment with sulfuric acid preceded the Kekulé formulation of the structure of benzene. The pinacol rearrangement and related rearrangements[3] such as Wagner-Meerwein rearrangements are now considered to proceed *via* carbenium ions [eq. (a)], electron deficient carbon



(a)

atoms, or non-classical ions *(1)*[4]. The details of such rearrangements have fired the imagination of chemists and aroused controversy now for over one hundred years.



(1)

Some time ago it occurred to the author that a related rearrangement of carbanions [eq. (b)] or organometallic compounds of the alkali metals might be of interest. Rearrangements of this type were already known in systems involving hetero atoms—the Stevens and Sommelet rearrangements of quaternary ammonium ions and the Wittig rearrangement



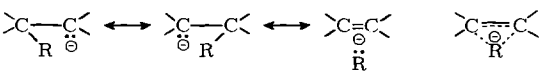
(b)

of ethers; however, the hetero atom in the known examples appears to play an important role since a bond to the hetero atom is broken during rearrangement. This review will be concerned chiefly with systems in which the organic moiety of the organoalkali compound contains only carbon and hydrogen.

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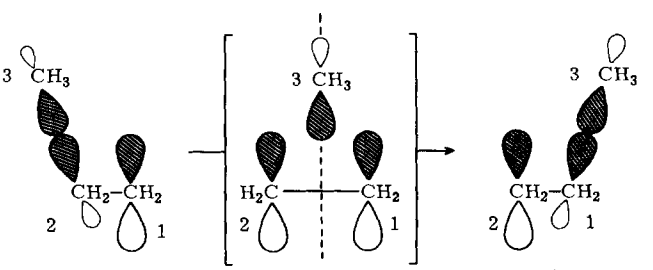
2. Molecular Orbital Considerations for [1,2] Sigmatropic Rearrangements of Carbanions

In terms of the simple qualitative theory of resonance between valence bond structures *(2)*—*(4)* or the equivalent hybrid structure *(5)* for the transition state (or intermediate) in the rearrangement of eq. (b), it is by no means obvious that rearrangements of carbanions (similarly, free radicals) should not be as common as rearrangements of carbenium ions[5]. Hence the application of Hückel molecular orbital (HMO) theory[6] to this problem by *Zimmerman* and *Zweig*[7] in 1961 represented a considerable advance in theory and was prescient of further developments by *Woodward* and *Hoffmann*[8,9].

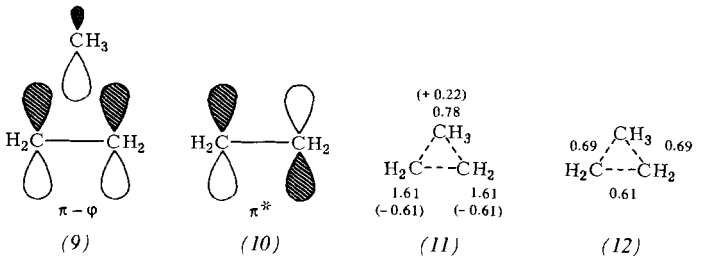


(2) *(3)* *(4)* *(5)*

The simplest example is illustrated by calculations upon the *n*-propyl anion which rearranges *via (7)*; the orbitals used in the calculation are shown schematically in terms of the appropriate basis sets. Since the transition state *(7)* has



a symmetrical distribution of atomic nuclei with respect to the plane (represented by the dotted line) which bisects the ethylene and methyl moieties, the allowable molecular orbitals for *(7)* must be either symmetric or antisymmetric with respect to this symmetry element. Hence the only allowed combination of orbitals are the bonding combination $\pi + \varphi$ (where π denotes the contribution from the ethylene π moiety and φ the sp^3



(9) (10) (11) (12)

Electron distribution (Net charge) Bond orders

orbital of the methyl group) and the two antibonding combinations $\pi-\varphi$ *(9)* and π^* *(10)*. The energies and coefficients of these orbitals may be obtained from a detailed HMO calculation; when the parameters of *Zimmerman* and *Zweig*[7] are used the net electron distribution may be calculated as in *(11)* and the bond orders as in *(12)* for the anion. The diagram for molecular orbital following[10] of reaction *(6)*→ *(8)* is given in Figure 1.

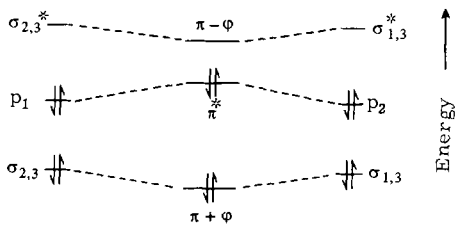
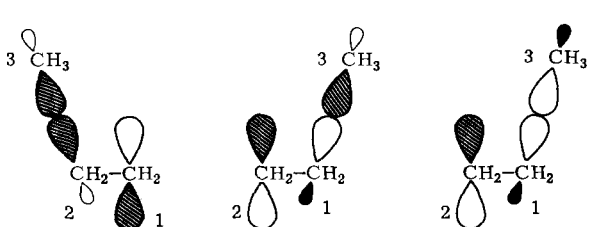


Fig. 1. Energy-molecular orbital diagram for [1,2] sigmatropic rearrangement of methyl in *n*-propyl anion *(6)*.

According to this calculation the transition state for methyl migration is some 1.13β units[11] higher in energy than the *n*-propyl anion. The qualitative explanation is that the 1,2-alkyl shift involves electrons moving into the antibonding π^* orbital with consequent weakening of the bond between C-1 and C-2 [see *(12)*[14]]. Hence *Zimmerman* and *Zweig*[7] concluded that "simple alkyl migration of carbanions ... may never be observed except under extreme conditions."

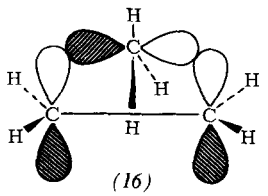
An alternative way of examining the [1,2] sigmatropic shift of methyl in *n*-propyl anion is that while the bonding orbital ($\sigma_{2,3}+p_1$) of the reactant *(6)* correlates with the bonding orbital ($p_2+\sigma_{1,3}$) of the product *(8)*, the other bonding orbital of the reactant *(13)* ($\sigma_{2,3}-p_1$) correlates with the antibonding orbital ($p_2-\sigma^*_{1,3}$) of *(14)* rather than the more stable bonding orbital ($p_2-\sigma_{1,3}$) of *(15)*. (In this approach of *Woodward* and *Hoffmann*[8] the local symmetry of composite atomic orbitals is utilized since the reactant and product do not possess relevant molecular symmetry elements.) This reaction is accordingly said to be symmetry-forbidden by the principle of conservation of orbital symmetry.



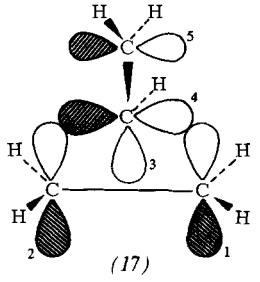
(13) (14) (15)

From yet another viewpoint due to *Evans*, *Dewar*, and *Zimmerman*[12] the transition state *(7)* for migration of methyl in *n*-propyl anion consists of a Hückel array of orbitals containing $4n$ or four electrons; hence the transition state is antiaromatic or destabilized relative to *n*-propyl anion. The transition state may be likened to molecules such as cyclobutadiene and cyclopropenyl anion which, as judged sometimes by derivatives, are known to be antiaromatic[13].

Are all [1,2] sigmatropic rearrangements of carbanions forbidden as thermal processes by molecular orbital considerations? The answer to this question by the Woodward-Hoffmann rules is that while suprafacial-suprafacial processes are forbidden, suprafacial-antarafacial processes are allowed [see *(7)*]. As alternatively stated by *Zimmerman*[15], the basis set of orbitals needs to contain one sign inversion since then it would constitute a Möbius array containing four (in general, $4n$) electrons and would be expected to be stable or aromatic. A conformation with such a sign inversion for methyl migration in *n*-propyl anion is shown in *(16)*; however, this conformation, which constitutes an inversion in configuration at the migrating methyl group, has obvious steric difficulties in that two of the hydrogens of the migrating group appear to undergo severe van der Waals repulsions with the carbon atoms of the ethylene moiety. While other conformations



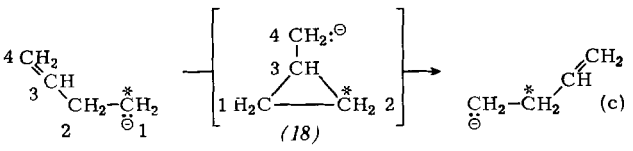
(16)



(17)

for methyl migration may be considered, all which involve one sign inversion in the basis set of orbitals appear to be of high energy content either because of repulsion between nuclei or poor overlap of orbitals.

A method of avoiding the steric repulsions in *(16)* is to have for the migrating group an atom of lower coordination number, *e.g.* an sp^2 hybrid atom as in the migration of vinyl or phenyl. The basis set of orbitals for the transition state (or intermediate) for vinyl migration [eq. (c)] is shown



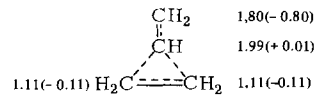
(18)

in *(17)*. An HMO calculation for *(17)* with parameters like those of *Zimmerman* and *Zweig*[7] is summarized in Table 1; apparently this calculation has not appeared elsewhere[16].

Table 1. Molecular orbitals for the transition state (or intermediate) *(17)* for vinyl migration [eq. (c)].

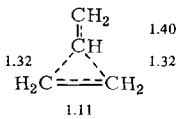
ψ	1	2	3	4	5	Energy [β units]
1	0.552	0.552	0.626	0	0	2.28
2	0.305	−0.305	0	0.784	0.512	1.45
3	0.396	−0.396	0	0.225	−0.798	−0.28
4	0.443	0.443	−0.780	0	0	−1.47
5	0.501	−0.501	0	−0.630	0.319	−1.98

The highest filled molecular orbital for vinyl migration (ψ_3) is of considerably lower energy ($-0.28\,\beta$) than that for methyl migration ($-0.81\,\beta$). The electron distribution for population of the three lowest lying orbitals is as shown in *(19)* while the bond orders[17] are as in *(20)*. Comparison with *(11)*



(19)

Electron distribution (Net charge)

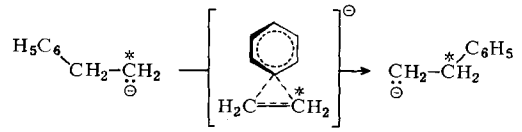


(20)

Bond orders

and *(12)* (methyl migration) shows that for vinyl migration most of the net negative charge is on C-4 as in the valence-bond structure *(18)* rather than on C-1 and C-2 as in *(11)*. Also the bond order is greater than unity everywhere in *(20)* rather than less than unity as in *(12)*. Indeed migration of vinyl in the homoallyl anion [eq. (c)] to give *(18)* is now computed to be *exothermal* by $0.67\,\beta$ whereas methyl migration of *n*-propyl anion to *(7)* was computed to be *endothermal* by $1.13\,\beta$. Also correlation of orbitals according to localized symmetries by the molecular orbital following technique now leads to the conclusion that vinyl migration is an allowed process[10]. It should be pointed out that less complete molecular orbital correlations which consider only the highest filled molecular orbital of the reactant (most simply the orbital containing the non-bonding electron pair on C-1) and of the intermediate *(17)* might have led to the conclusion that the reaction was forbidden since a non-bonding orbital of the reactant correlates with an anti-bonding orbital (ψ_3) of the intermediate. Also it is not *a priori* obvious whether *(17)* constitutes a Möbius array ($\varphi_1+\varphi_2+\varphi_4+\varphi_5$) or a Hückel array ($\varphi_1+\varphi_2+\varphi_3$) of orbitals, since in fact it contains both basis sets, or whether the number of electrons belonging to each array is $4n$ or $2+4n$ electrons. To be sure, detailed calculations (Table 1) do reveal that for the ground state two electrons are assigned to the Hückel system and four electrons to the Möbius system as expected for a stable (or "aromatic") transition state or intermediate. More simply still *(17)* might have been regarded as a rather stable structure since at least one reasonably stable valence-bond structure *(18)* may be written for it.

Molecular orbital considerations for phenyl migration [eq. (d)] are similar to those for vinyl migration except that the negative charge in the intermediate or transition state *(21)* is more highly delocalized somewhat at the expense of the conjugated π system of the benzenoid ring. *Zimmerman* and



(d)

(21)

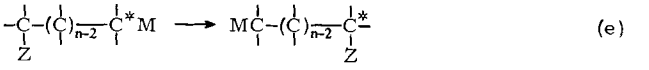
Zweig[7] calculated that migration of phenyl in β-phenylethyl anion to give *(21)* was exothermal by $0.52\,\beta$ units or somewhat less exothermal than vinyl migration as estimated above.

A qualitatively most interesting result of these simple molecular orbital calculations is that they predict[7] that, other factors being equal, [1,2] sigmatropic rearrangements will occur with decreasing ease along the series: carbenium ion > free radical > carbanion since, in general, for free radical and carbanion rearrangements a non-bonding orbital in the reactant is converted into an antibonding orbital in the intermediate or transition state. The antibonding orbital is not occupied for carbenium ions while it is doubly occupied for carbanions. The calculation also suggests that, once a carbanion rearrangement has been identified, the corresponding free radical rearrangement should occur and, with less certainty, *vice versa*.

A chemist who does not believe that molecular orbital theory is the greatest advance in organic chemistry since the introduction of valence-bond (Kekulé) structures might question the conclusions from the present calculations. Indeed most chemists need to be concerned with the approximations involved. Of immediate concern is whether the correct resonance integrals have been chosen; *Phelan*, *Jaffé*, and *Orchin*[18] have repeated many of the present calculations with different resonance (and Coulomb) integrals and obtained different quantitative results although most of the qualitative conclusions are unaffected. Another problem is whether all of the relevant orbitals have been included in the calculations. For example in *(7)* why not consider the σ-bond linking C-1 to C-2 in the basis set of orbitals? Indeed inclusion of this orbital in simple HMO calculations leads to the conclusion that methyl migration in *n*-propyl anion to give the bridged species *(7)* would be exothermal by some $0.21\,\beta$ units; however, one might question whether such a calculation which concentrates yet more charge on atoms C-1 and C-2 (albeit on more orbitals) and which does not take into consideration electron repulsion could represent an improved calculation. A still approximate but more advanced molecular orbital calculation[19,20] (CNDO/2) gives the result that methyl migration in *n*-propyl anion to the bridged species *(7)* should be endothermal by some 24 kcal/mol. In addition to the approximations which are inherent to the calculations themselves, chemists must question any calculations for carbanions which neglect the counterion and the solvent surrounding the ions. Nevertheless molecular orbital calculations have been of considerable heuristic value and on the whole have correlated experimental results as is shown by the following summary on rearrangements of organoalkali compounds.

3. Experimental Results upon [1,*n*] Sigmatropic Rearrangements of Carbanions

In this section [1,*n*] sigmatropic rearrangements of the type



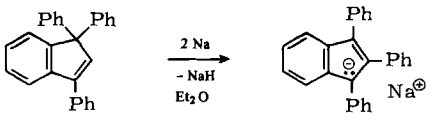
(e)

will be reviewed according to the nature of the migrating group Z (*e.g.*, Z = phenyl, vinyl, or alkyl). The chain of atoms over which Z migrates will normally be a saturated carbon chain but will include in some examples hetero atoms and

multiple bonds. While this survey emphasizes rearrangements of organoalkali compounds, some related rearrangements of Grignard reagents will be included for comparison.

3.1. Migrations of Aryl Groups[21]

The earliest known example of skeletal rearrangement of an organoalkali compound appears to be the rearrangement of 1,1,3-triphenylindene *(22)* by sodium which was discovered, but misinterpreted, by *Schlenk* and *Bergmann*[22] and reinterpreted by *Ziegler* and *Crossman*[23] to involve phenyl migration as shown in equation (f). In a reinvestigation of this reaction *Miller* and *Boyer*[24] suggested that the rearrangement occurs in a radical anion of *(22)*, although rearrangement of the disodium adduct of *(22)* was not excluded by the available



(f)

(22)

evidence. Since rearrangement of a radical anion may be looked upon as rearrangement of a free radical, reaction (f) does not necessarily exemplify rearrangement of a carbanion.

The first example of rearrangement of a simple carbanion [eq. (e), $n=1$] with all carbon skeleton was provided by rearrangement during the reaction of 2-chloro-1,1,1-triphenylethane *(23)* with sodium in ethereal solvents; this reaction was discovered by the author[25], and independently, essentially at the same time, by *Zimmerman* and *Smentowski*[26]. That this reaction involved formation of an intermediate organosodium compound *(24)* prior to rearrangement was demonstrated[25] by carrying out the reaction in dioxane containing

$$\underset{(23)}{Ph_3C{-}CH_2Cl} \xrightarrow[-NaCl]{2\,Na} \underset{(24)}{Ph_3C{-}CH_2Na} \rightarrow Ph_2\overset{\ominus}{C}{-}CH_2Ph \quad (\overset{\oplus}{Na})$$

a little *tert*-amyl alcohol, whereupon the reaction product was primarily 1,1,1-triphenylethane. In contrast, if *tert*-amyl alcohol was added after reaction with sodium, 1,1,2-triphenylethane was the dominant product. Similarly cleavage[27] of the chloride *(23)* or of 2,2,2-triphenylethyltrimethylammonium iodide *(25)* with sodium in liquid ammonia gave

$$Ph_3C{-}CH_2\overset{\oplus}{N}(CH_3)_3\ I^{\ominus} \quad (25)$$

primarily 1,1,1-triphenylethane accompanied by some 11% of 1,1,2-triphenylethane. The 2,2,2-triphenylethyl group in *(25)* cleaves from quaternary nitrogen 10^4 times more readily than methyl or 10^6 times more readily than ethyl[28]. If the relative rates of cleavage of primary, secondary, and tertiary alkyl groups from quaternary nitrogen can be taken as a guide[28] to the mechanism of cleavage, primary alkyl groups cleave directly as carbanions rather than free radicals. Accordingly the cleavage of *(25)* is interpreted as giving initially the 2,2,2-triphenylethyl anion which is largely protonated by ammonia prior to rearrangement. The much more facile cleavage of the 2,2,2-triphenylethyl group as compared with that of ethyl is evidently due to the ability of phenyl groups to stabilize a negative charge upon the triphenylethyl group; it cannot arise from a direct neighboring group participation of phenyl during cleavage (cf. the 4×10^6 anchimeric acceleration[29] in solvolysis with carbenium ion rearrangement of 2,2,2-triphenylethyl brosylate) since most of the final hydrocarbon product is of unrearranged structure. This example does illustrate the conclusion from molecular orbital calculations that, even in a favorable case for rearrangement of carbanions, rearrangements of carbenium ions occur with considerably greater facility than rearrangements of carbanions such that rearrangement of a carbanion may occur in a concerted process with formation of the carbenium ion.

More direct evidence for formation of an organoalkali compound prior to rearrangement is provided by reaction[30] of the chloride *(23)* with lithium metal in tetrahydrofuran (THF) at -65 to -30°C to give 2,2,2-triphenylethyllithium which is comparatively stable at low temperature but rearranges rather readily at 0°C or higher to give 1,1,2-triphenylethyllithium. In contrast potassium[30] in 1,2-dimethoxyethane at -50°C or Cs-K-Na alloy[31,32] in THF at -65°C gives almost instantly rearranged 1,1,2-triphenylethyl-potassium or -cesium. Bis(2,2,2-triphenylethyl)mercury reacts[33] with butyllithium in THF below 0°C to give 2,2,2-triphenylethyllithium which rearranges at higher temperature to 1,1,2-triphenylethyllithium [eq. (g)].

$$(Ph_3C{-}CH_2)_2Hg \xrightarrow{BuLi} Ph_3C{-}CH_2Li \rightarrow LiCPh_2{-}CH_2Ph \quad (g)$$

Also 2,2,2-triphenylethyllithium reacts[34] with excess potassium *tert*-butoxide at -75°C in THF to give complete rearrangement in less than 10 minutes; evidently this rearrangement goes by the process[35] outlined in eq. (h).

$$Ph_3C{-}CH_2Li \xrightarrow{KO\,tBu} Ph_3C{-}CH_2K \rightarrow KCPh_2{-}CH_2Ph \quad (h)$$

The above summary of experimental work provides compelling evidence that 2,2,2-triphenylethylalkali compounds are rearrangement precursors; however, the circumstance that rearrangement starts and ends with an organoalkali compound does not prove[36] that the rearrangement itself directly occurs in an organoalkali compound or in an anion derived from the organoalkali compound. For example, the rearrangement might occur in an intermediate free radical or methylene. Also the rearrangement might occur by an inter- rather than an intra-molecular process as implied by our previous molecular-orbital considerations. What evidence is available concerning the detailed mechanism of migration of aryl groups in organoalkali compounds?

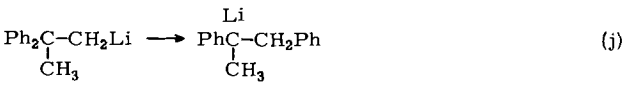
A possible mechanism for phenyl migration in 2,2,2-triphenylethyllithium would be by an elimination-readdition process [eq. (i)]. As a test for this mechanism 2,2,2-triphenylethyl-

$$Ph_3C{-}CH_2Li \rightarrow Ph_2C{=}CH_2 + PhLi \rightarrow LiCPh_2{-}CH_2Ph \quad (i)$$

lithium was allowed[37] to undergo rearrangement in the presence of ^{14}C-labeled phenyllithium or in the presence of the much more reactive[38] benzyllithium. There was no detectable incorporation of radioactive phenyl or of benzyl group in the product of rearrangement. While these experiments help establish that rearrangement of 2,2,2-triphenylethyllithium

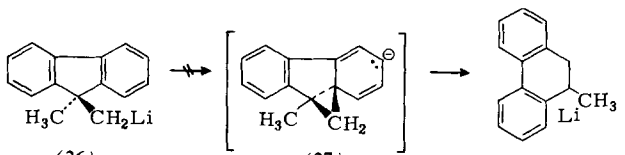
occurs by an *intramolecular* process, they do not eliminate some subtle modifications of the elimination-readdition process. For example, 2,2,2-triphenylethyllithium may eliminate phenyl anion to give 1,1-diphenylethene; the phenyl anion and 1,1-diphenylethene may exist in a solvent "cage" and recombine before radioactive phenyllithium or benzyllithium can penetrate the "cage".

Zimmerman and *Zweig*[7] have reported that 2,2-diphenylpropyllithium, prepared by reaction of lithium metal with 1-chloro-2,2-diphenylpropane or with bis(2,2-diphenylpropyl)-mercury, rearranges at reflux temperature in diethyl ether to give 1-methyl-1.2-diphenylethyllithium [eq. (j)]. In contrast



(j)

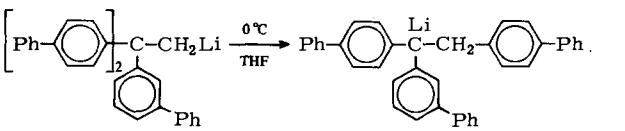
Eisch and *Kovacs*[33] find that the rather similar organolithium compound *(26)* did not rearrange to *(28)*, presumably because rearrangement requires production of the highly strained spiro



(26) *(27)*

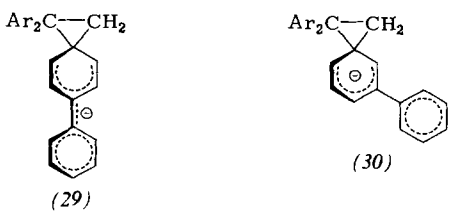
intermediate *(27)*. If aryl migration proceeded by an elimination-readdition process, there is no apparent reason why rearrangement of *(26)* to *(28)* should not have occurred.

Positive evidence in favor of spiro intermediates or transition states during aryl migrations is found[39] in the highly preferential migration of *p*-biphenylyl as opposed to *m*-biphenylyl in 2-*m*-biphenylyl-2,2-bis(*p*-biphenylyl)ethyllithium *(28)*. This



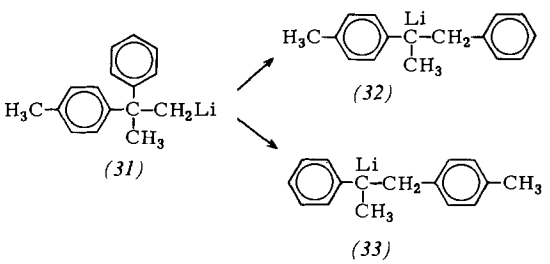
(28) > 98%

result can be explained on the basis that the rearrangement can proceed much more readily *via* the transition state or intermediate *(29)* than *via (30)* because of the more extensive charge delocalization in the *p*-phenyl group of *(29)* compared with that in the *m*-phenyl of *(30)*. Had the organolithium compound rearranged by elimination of a biphenylyl anion or radical little difference in migratory aptitude of *m*- and *p*-biphenylyl groups would have been expected.



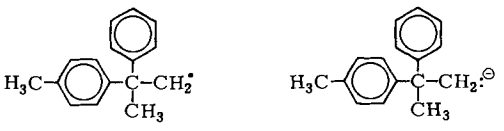
(29) *(30)*

In view of what is expected from molecular orbital considerations for the comparative ease of migration of carbanions *versus* free radicals, what is the evidence that aryl migration occurs in an anion (or organoalkali compound) rather than a free radical? *Zimmerman* and *Zweig*[7] have shown that 2-phenyl-2-*p*-tolylpropyllithium *(31)* rearranges in ethereal solution at reflux temperature with formation of about a 11:1 ratio of the product of phenyl migration *(32)* to the product of *p*-tolyl migration *(33)*. If rearrangement of *(31)*



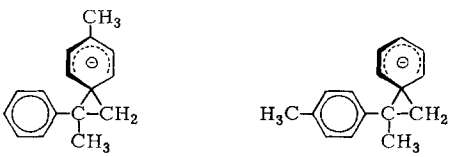
(31) *(32)* *(33)*

occurred in the intermediate free radical *(34)*, no appreciable selectivity would be expected in the migration of phenyl *versus* *p*-tolyl (in the rearrangement of neophyl radicals[40], the *p*-tolyl



(34) *(35)*

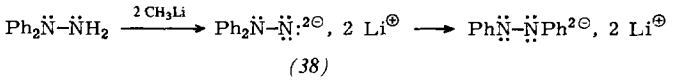
group migrated about 0.7 times as fast as phenyl). If rearrangement occurred in the carbanion *(35)*, *p*-tolyl would be expected to migrate appreciably more slowly than phenyl since the expected intermediate or transition state *(36)* for *p*-tolyl migration should be less stable than that for phenyl migration *(37)* (toluene is reported[41] to be some 19 times more acidic per



(36) *(37)*

methyl hydrogen than *p*-xylene). Hence the relative ease of migration of *p*-tolyl *versus* phenyl in *(31)* argues strongly in favor of this rearrangement being a carbanion rearrangement rather than a free radical rearrangement.

Other examples of [1,2] migrations of aryl groups in organoalkali compounds could be cited[21]. Such rearrangements appear to be a general phenomenon and also occur in various hetero-atom analogs. A notable case is exemplified by the dianion of 1,1-diphenylhydrazine *(38)* which rearranges[42] slowly but quantitatively in diethyl ether at 30°C



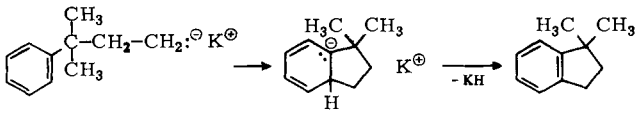
(38)

whereas the corresponding monoanion (as lithium salt) does not undergo [1,2] phenyl migration even at 100°C in bis(2-methoxyethyl) ether.

Sigmatropic aryl shifts of order [1,3] should occur in organoalkali compounds in principle but appear never to have been observed because of competing reactions. Thus 3,3,3-triphenylpropyllithium[43] in THF at −40°C undergoes fragmentation [eq. (k)]. In liquid ammonia the 3,3,3-triphenylpropyl anion from cleavage of 3,3,3-triphenylpropyltrimethyl-

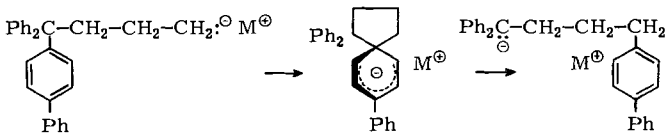
$$Ph_3C{-}CH_2{-}CH_2{-}Li \rightarrow Ph_3CLi + CH_2{=}CH_2 \qquad (k)$$

ammonium iodide with sodium undergoes primarily protonation to 1,1,1-triphenylpropane in addition to a little fragmentation[27]. The 3-methyl-3-phenylbutyl anion *(39)*, formed evidently in reaction of isopropylbenzene at 190°C with potassium-anthracene catalyst under some 30 atmospheres pressure of ethylene, undergoes cyclization to the indan *(41)* in about 50% yield, evidently by way of the intermediate *(40)*[44].



(39) *(40)* *(41)*

Sigmatropic aryl shifts of order [1,4] have been observed in reactions of organoalkali compounds in a number of instances. Whereas 4,4,4-triphenylbutyllithium in THF gave primarily 1,1,1-triphenylbutane but no product of [1,4] rearrangement of phenyl when warmed to 25°C, the corresponding organo-potassium compound gave a low yield of 1,1,4-triphenylbutyl anion from [1,4] migration of phenyl in addition to chiefly 1,1-diphenyl-1,2,3,4-tetrahydronaphthalene (product from *ortho* cyclization of the anion) and a little 1,1,1-triphenylbutane[31]. A high yield of 4-*p*-biphenylyl-1,1-diphenylbutyl anion (product of [1,4] migration of *p*-biphenylyl) was obtained from reaction of 4-chloro-1-*p*-biphenylyl-1,1-diphenylbutane in THF with potassium, cesium, or Cs-K-Na alloy[45]. Since in presence of active proton donors such as *tert*-butyl alcohol, the product was largely unrearranged 1-*p*-biphenylyl-1,1-diphenylbutane (or products derived therefrom), the reaction is believed to proceed by way of 4-*p*-biphenylyl-4,4-diphenylbutylalkali metal compounds *(42)*. Even in a reaction time of two minutes at −75°C it was not possible to detect the suspected spiro intermediate *(43)*

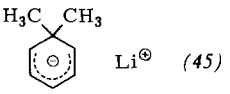


(42) *(43)* *(44)*

which evidently suffers facile ring opening to *(44)*. The relative rate of [1,4] migration of *p*-biphenylyl *versus* protonation of the organoalkali compound *(42)* by solvent was found to increase rapidly along the series: Li ≪ Na ≪ K or Cs. Also [1,4] migration of aryl competes less favorably in competition with protonation than does [1,2] migration. In other work[31] [1,5] migration of phenyl was somewhat less favorable than [1,4] migration in rearrangements of organoalkali compounds in THF.

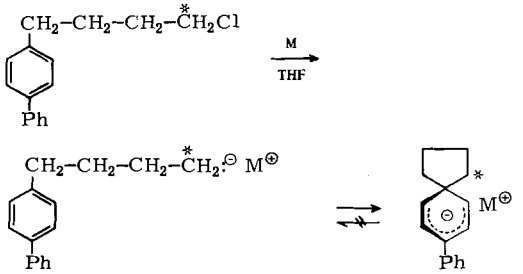
In the forgoing discussion we have considered spiro anions [cf. *(21)*, *(27)*, *(29)*, *(30)*, *(36)*, *(37)*, *(43)*] to be intermediates or transition states for [1,*n*] sigmatropic rearrangements of aryl. Is there any direct evidence bearing on this point? HMO calculations suggest that spiro anions might be stable intermediates in rearrangements of carbanions (see Section 2). The failure to observe such intermediates in all of the forgoing work could be attributed either to inadequate calculations (especially the neglect of solvation and cation-anion interactions) or to the fact that while spiro anions are more stable than the initial anions, they are in all cases so far considered less stable than the open product anions. Both explanations are probably of importance.

The successful preparation[46] of various pentadienyllithiums including 6,6-dimethylcyclohexadienyllithium *(45)* by



(45)

reaction of 1,4-dienes with *n*-butyllithium in THF encouraged us to attempt the detection of spiro anions in what would otherwise be [1,*n*] sigmatropic migration of aryl groups. While the spiro anion *(43)* was too unstable for detection even at −75°C, we have been able to prepare the related spiro anion *(47)* from reaction[47] of the corresponding chloride with cesium or potassium in THF. Anion *(47)* was characterized both on the basis of its NMR spectrum and from its products of carbonation and protonation. That anion *(46)*

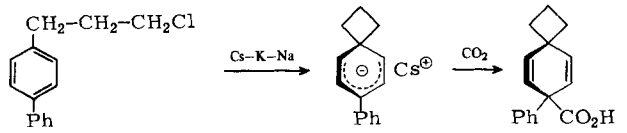


(46) *(47)*

M = K, Cs

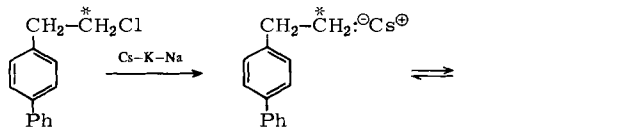
was a precursor of *(47)* was indicated by experiments in which various proton sources were able to "trap" *(46)* as 1-*p*-biphenylylbutane (or derivative) prior to cyclization. Interestingly anion *(47)* once formed did not reopen to *(46)* since deuterium labeling experiments (asterisks) gave no scrambling of the label in products derived from *(46)*. Indeed the anion *(47)* was moderately stable in THF even at 65°C and underwent other reactions such as protonation and polymerization faster than ring opening to regenerate *(46)*. Evidently the geminal phenyl groups of the spiro anion *(43)* greatly accelerate ring opening to give *(44)*; since these phenyl groups also accelerate ring closure[47] of *(42)* more than 240 fold (potassium as counterion), the subtle question of whether *(43)* is best described as an intermediate or transition state is unresolved.

In related experiments 1-*p*-biphenylyl-3-chloropropane was found to react[48] with Cs-K-Na alloy in THF at −75°C for one minute to give after carbonation the spiro acid *(49)* (36% yield); the cleavage product, *p*-biphenylylacetic acid (14%); the α-metalation product, 2-*p*-biphenylylbutanoic acid (3%); and the "normal" non-cyclized product, 4-*p*-biphenylylbutanoic acid (6%). The formation of *(49)* provides good evidence for the presence of the spiro anion *(48)* whose half-life was only some 13 minutes under the reaction conditions.

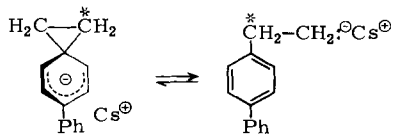


(48) (49)

In contrast, the reaction[48] of 1-*p*-biphenylyl-2-chloroethane with Cs-K-Na alloy in THF at −75°C for 1 minute before carbonation gave less than 1% (if any) of product expected from the spiro anion *(51)*, even though experiments[49] with the labeled compound 2-*p*-biphenylyl-1-chloro-1,1-dideuterioethane at −65°C suggest that 18 to 44% of spiro anion is formed as judged by the amount of deuterium scrambling in the product *p*-biphenylylethane. Evidently the spiro anion *(51)* is unstable with respect to the open anions *(50)* and *(52)*.



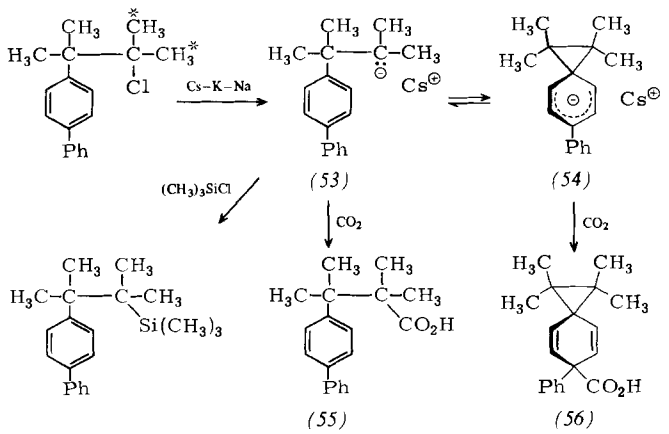
(50)



(51) (52)

Since *Maercker et al.*[50] were able to stabilize the cyclopropylmethyl form of the 3-butenyl Grignard reagent by introduction of two *gem*-dimethyl groups onto the cyclopropyl ring, we[48] undertook a related application of the Thorpe-Ingold effect. Reaction of 2-*p*-biphenylyl-3-chloro-2,3-dimethylbutane with Cs-K-Na alloy in THF at −75°C for one minute gave after carbonation 28% of the spiro acid *(56)* and 7% of 3-*p*-biphenylyl-2,2,3-trimethylbutanoic acid *(55)*. These products are evidently formed according to Scheme 1.

Scheme 1



(53) (54) (55) (56)

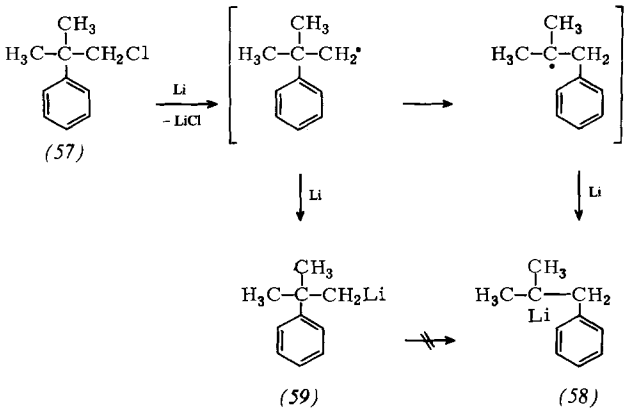
According to the results of carbonation the half-life of *(54)* is about 22 minutes at −75°C in THF. Interestingly, the open anion *(53)* seems to have the *same* half-life[51] as *(54)*. This result can be understood if *(53)* and *(54)* are in mobile equilibrium. Evidence in favor of an equilibrium comes from studies[51] with deuterium-labeled chloride (see asterisks). The resulting carboxylic acid *(55)* showed extensive deuterium label in the methyl groups nearest the biphenylyl group in about the amount expected for equilibration of the position of the label. For a mobile equilibrium *(53)*⇌*(54)*, certain electrophilic reagents may attack one of the isomeric anions more readily than the other; this is the approach used to explain the results of reaction[51] with trimethylsilyl chloride which yielded the normal product but no spiro cyclic derivative. Clearly the equilibrium between *(53)* and *(54)* needs to be studied also by spectroscopic techniques.

While the equilibrium mixture of *(53)* and *(54)* with cesium as counterion contains the anions in a ratio of about 1:4 (if the results of carbonation can be relied upon to supply such information), with lithium as counterion in THF only the open acid *(55)* is obtained upon carbonation. Evidently lithium ion prefers to interact with the localized anion *(53)* since such interaction can lead to the usual covalent organolithium compound. Somewhat similar results were obtained by *Maercker* and *Roberts*[52] in their studies upon cation effects in the cyclopropylmethyl-homoallyl rearrangement.

The work cited here on direct observation of spiro anions from reaction of arylalkyl chlorides with alkali metals, along with work[53] on related heteroatom analogs, establishes spiro anions as plausible intermediates during aryl migrations in organoalkali compounds. To be sure, what is more simply described, by analogy with model compounds, as a transient reaction intermediate may in some cases later be found to be better described as a transition state.

A warning needs to be sounded concerning rearrangements in reaction of alkali metals with alkyl halides: the observed rearrangements are *not* necessarily all rearrangements of organoalkali compounds. For example, reaction[54] of neophyl chloride *(57)* with lithium in THF at −65°C for 30 minutes gives 6% of 1,1-dimethyl-2-phenylethyllithium *(58)* in addition to the normal product 2-methyl-2-phenylpropyllithium *(59)*. The normal product *(59)*, however, does *not* rearrange to *(58)* under the reaction conditions for formation of *(58)*.

If the observed rearranged product came not from rearrangement of an organolithium compound, whence did it come? A reasonable explanation is that reactions of alkyl halides with lithium metal occur by way of intermediate radicals which in part are free enough from the metal surface to rearrange. This conclusion agrees with molecular orbital considerations (see Section 2) which suggest that free radical rear-



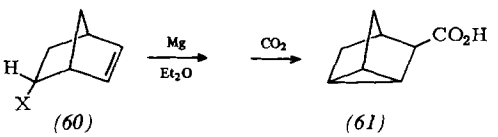
(57) (59) (58)

rangements should occur more readily than rearrangements of carbanions. In the case of reaction[45] of 1-*p*-biphenylyl-4-chloro-1,1-diphenylbutane with lithium metal in THF at −75 °C, the organolithium product contained up to 47% of the rearranged product 4-*p*-biphenylyl-1,1-diphenylbutyllithium [cf. *(44)*]; again the normal product 4-*p*-biphenylyl-4,4-diphenylbutyllithium did not undergo rearrangement under the conditions of its preparation.

Better yields of normal as opposed to rearranged organolithium compounds are obtained[45] by use of homogeneous solutions of lithium dihydrobiphenylylide in THF as reducing agent for alkyl chlorides rather than lithium metal; evidently this lithium carrier more readily donates lithium atoms to intervening free radicals than does lithium metal itself. In our experience molten alkali metals (Na, K, Cs) in ethereal solvents normally react with alkyl halides with little rearrangement prior to formation of organoalkali compounds; this conclusion rests upon "trapping" of intervening organoalkali compounds by proton donors. At least for cesium and Cs-K or Cs-K-Na alloys the efficacy in reducing expected intermediate radicals to organoalkali compounds prior to rearrangement may rest upon the solubility of cesium in tetrahydrofuran (blue solution especially at low temperatures). Potassium is also said[55] to be slightly soluble in tetrahydrofuran although we have never been able to detect the claimed blue color in the purified solvent even at low temperatures; blue solutions[30] of potassium are clearly visible in cold 1,2-dimethoxyethane.

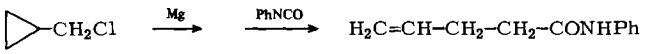
3.2. Migrations of Vinyl Groups

Aryl and vinyl groups frequently display similar behavior in chemical reactions; nevertheless, the discovery of vinyl migration in organometallic compounds of the alkali metals was entirely independent of work upon aryl migrations. Indeed early pertinent work was in the area of Grignard reactions. In 1950, *Roberts, Trumbull, Bennett,* and *Armstrong*[56] noted cyclopropane ring formation during Grignard reactions of *endo*-norbornenyl halides [*(60)* → *(61)*].



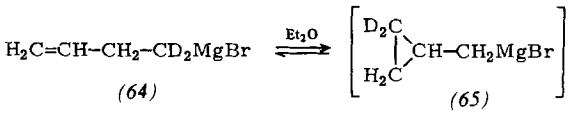
(60) *(61)*

Roberts and *Mazar*[57] observed the reverse reaction of cyclopropylmethyl chloride *(62)* with magnesium to give ring-opened product *(63)*; however, it was not clear at which



(62) *(63)*

step of the Grignard sequence rearrangement occurred. The full import of these observations became apparent in 1960 when *Silver, Shafer, Norlander, Rüchardt,* and *Roberts*[58] unequivocally demonstrated by NMR spectroscopy (in addition to chemical methods) that labeled homoallyl Grignard reagent *(64) itself* undergoes a [1,2] migration of a vinyl group to give *(66)*. Since the Grignard reagent from *(62)* existed only in the open form according to its NMR spectrum, cyclopropylmethyl Grignard reagent *(65)* was assumed to be the intermediate in the conversion of *(64)* into *(66)*. The reasonableness of this assumption was strengthened by partial "trapping" of cyclopropylmethylmagnesium chloride as cyclopropylmethane during reaction of *(62)* with magnesium in diethyl ether containing benzoic acid; also the magnesium bromide corresponding to *(62)* could be prepared in dimethyl ether at −24 °C and observed to rearrange to 3-butenylmagnesium bromide[59].

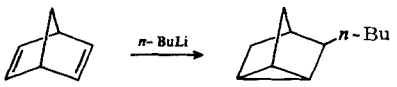


(64) *(65)*

$\rightleftharpoons$ $H_2C{=}CH{-}CD_2{-}CH_2MgBr$

(66)

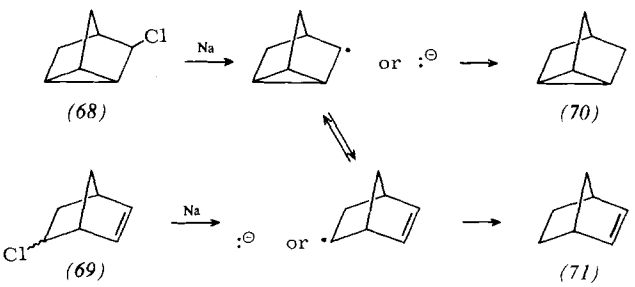
The extension of this work to corresponding organolithium compounds was perhaps implicit in the report of *Wittig* and *Hahn*[60] on the addition of *n*-butyllithium to norbornadiene to give among other products 3-*n*-butylnortricyclene *(67)*.



(67)

The full demonstration was provided by *Lansbury et al.*[61] who prepared cyclopropylmethyllithium by a lithium-halogen exchange at −70 °C and observed its isomerization to 3-butenyllithium. The isomerization was faster in diethyl ether than in a 10:1 mixture of petroleum ether and diethyl ether; also tetrahydrofuran was more effective than diethyl ether in promoting the isomerization.

Freeman et al.[62] found that the reaction of nortricyclyl chloride *(68)* and of norbornenyl chloride (50% *endo*, 50% *exo*) *(69)* with sodium in decane at 85—90 °C gave about the same mixture of nortricyclene *(70)* and norbornene *(71)* (in ratios of 71:10 and 49:10, respectively). They noted that

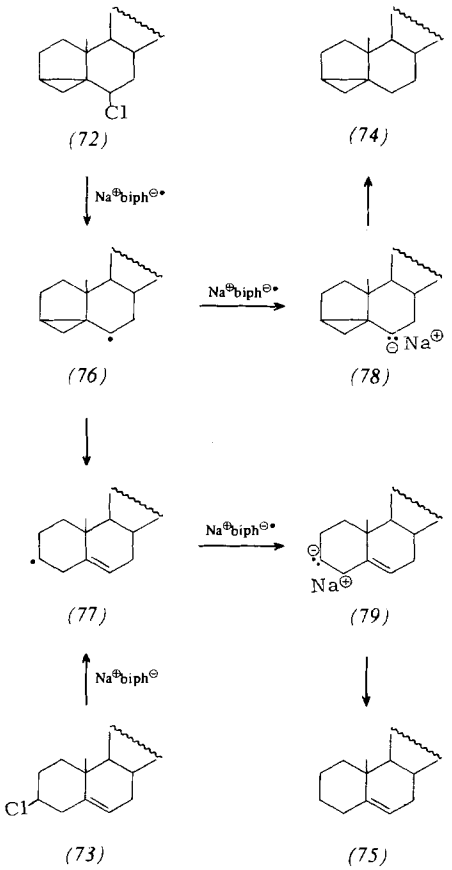


(68) *(70)*

(69) *(71)*

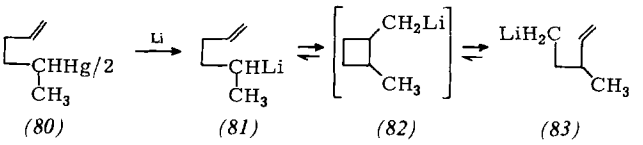
these products could be attributed to an equilibrium between cyclopropylmethyl and homoallyl anions; however, equilibrium between free radical intermediates analogous to the anions remained an alternative mechanistic possibility. That the latter interpretation is perhaps correct is indicated by the work of *Cristol* and *Barbour*[63] upon 3,5-cyclocholestanyl chloride *(72)* and cholesteryl chloride *(73)* with sodium dihydrobiphenylylide in various solvents containing 1,2-dimethoxyethane. While cholesteryl chloride *(73)* gave only 5-choles-

tene *(75)*, *(72)* gave mixtures of 3,5-cyclocholestane *(74)* and 5-cholestene in ratios *(74)*:*(75)* which increased with the effective concentration of sodium dihydrobiphenylylide but were independent of the hydrogen-atom donating ability of the solvent. These results were reasonably interpreted on the basis that intermediate classical radicals were first formed.



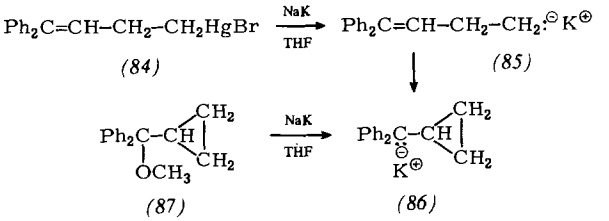
The radical *(76)* either rearranges to *(77)* or undergoes "capture" by sodium dihydrobiphenylylide to give organosodium compound *(78)* which is ultimately protonated prior to appreciable rearrangement to *(79)*. Similar interpretations and results were obtained by *Garst*, *Ayers*, and *Lamb*[64] for the reaction of sodium dihydronaphthylide with 5-hexenyl and cyclopentylmethyl halides; in this case cyclization of the 5-hexenyl radical to the cyclopentylmethyl radical was observed whereas the corresponding anions only underwent protonation. These results suggest that radicals undergo cyclization more readily than carbanions in agreement with the HMO calculations of Section 2. The results taken in comparison with related work upon aryl migration suggest that, relative to corresponding rates of reduction to anions, vinylalkyl radicals undergo cyclization more readily than arylalkyl radicals undergo spirocyclization (however comparisons have never been made under identical experimental conditions); this conclusion is also in agreement with HMO calculations.

The reactions of unsaturated aliphatic halides with alkali metals are frequently complex; in addition to products from rearrangements of intermediate free radicals or carbanions, products from rearrangements of carbenes are sometimes found[65]. Presumably the [1,3] migration of vinyl observed[66] during the cleavage of the mercury compound *(80)* with

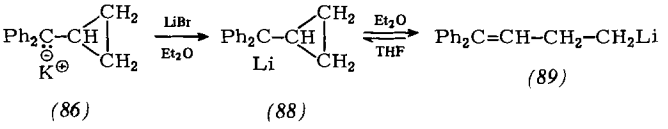


lithium in cyclohexane at reflux temperature occurred in intermediate organolithium compounds [*(81)* → *(83)*]; if so, the compound *(83)* is much more stable than *(81)* since at least 99 % of the C_6 product upon hydrolysis consisted of 3-methyl-1-pentene.

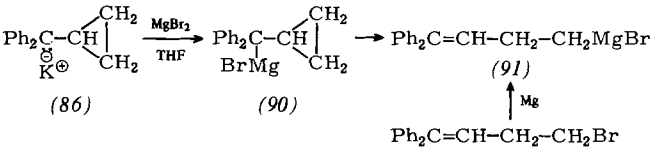
A detailed study of equilibria between the organometallic derivatives of cyclopropylmethyl and homoallyl compounds has been made by *Maercker* and *Roberts*[67]. Reaction of 4,4-diphenyl-3-butenylmercuric bromide *(84)* with Na-K alloy in THF gave only cyclopropyldiphenylmethylpotassium *(86)* according to the products of carbonation. No evidence was found for the open organopotassium compound *(85)* under these conditions.



The anion of *(86)* can also be generated by cleavage of the ether *(87)*. The structure of *(86)* is confirmed by its NMR spectrum. Reaction of *(86)* with lithium bromide in diethyl ether resulted in disappearance of the deep-red color of the anion; carbonation affords only diphenylallylacetic acid.

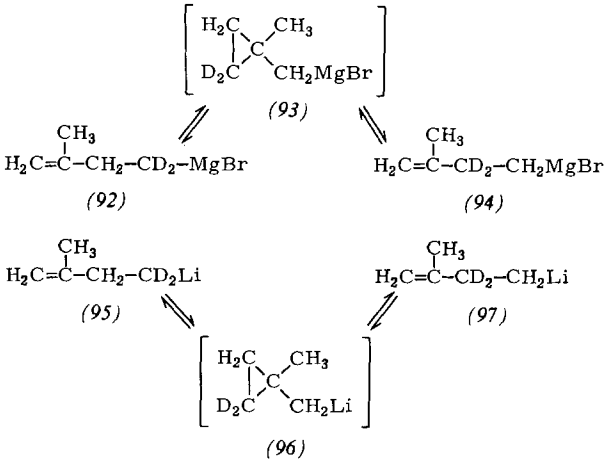


Hence in diethyl ether the open-chain lithium compound *(89)* predominates. Repetition of this experiment with lithium bromide in THF interestingly showed only the presence of *(88)*. In ether: tetrahydrofuran (2:1) the equilibrium mixture contained some 15 parts of *(88)* to 1 part of *(89)*. Reaction of *(86)* with magnesium bromide in THF gave the same Grignard reagent *(91)* as obtained from 4,4-diphenyl-3-butenyl bromide[68]; this Grignard reagent contains more than 99 % of the open form *(91)* in diethyl ether or in tetrahydrofuran.



These results were taken to mean that the open-chain lithium and magnesium compounds are truly covalent species while the cyclic lithium and potassium compounds are ionic species which are solvated. Better solvating solvents, tetrahydrofuran as opposed to diethyl ether, favor the ionic species with lithium as counterion.

The kinetics of vinyl migration in labeled 3-methyl-3-butenylmagnesium bromide *(92)* has been investigated by *Maercker* and *Weber*[69]. The postulated cyclopropylmethyl intermediates *(93)* and *(96)* could not be detected chemically

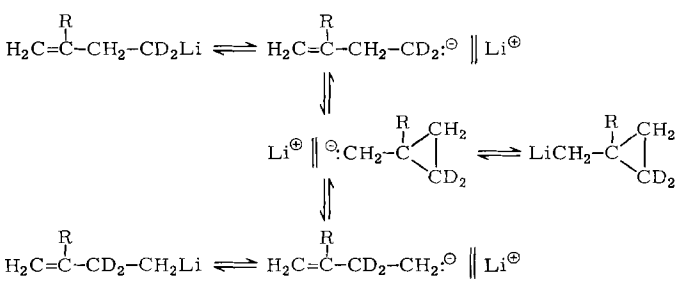


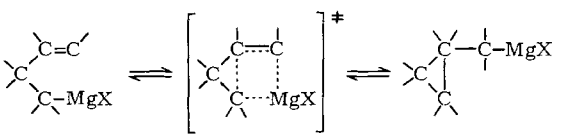
or by NMR spectroscopy. Hence the two phenyl groups of *(88)* must greatly stabilize the ionic intermediate by delocalization of the negative charge. The organolithium compound *(95)* rearranges much faster than the organomagnesium compound *(92)*. The calculated first-order rate constant for rearrangement of the organolithium compound was "largely independent of concentration" and increased with increasing solvating power of the solvent (cyclopentane < ether < THF); also addition of a little *N,N,N',N'*-tetramethylethylenediamine (TMEDA) greatly accelerated rearrangement. In contrast, *(92)* rearranged more readily in diethyl ether than in tetrahydrofuran; the calculated first-order rate constant for rearrangement increased with increasing concentration of *(92)* or of added magnesium bromide.

The kinetics of these rearrangements is complicated by molecular association of Grignard reagents[70] and organolithium compounds[71] in ethereal solvents and by irreversible reactions of organolithium compounds[72] with ethers. The kinetics of rearrangement of the organolithium reagent requires that the transition state of the rate-determining step be more highly solvated than the bulk of the reacting molecules. Within this broad category there are many detailed mechanisms possible within the restricted range of the kinetic studies. The simplest possibility, a slight modification of that of *Maercker* and *Weber*[69], is presented in Scheme 2.

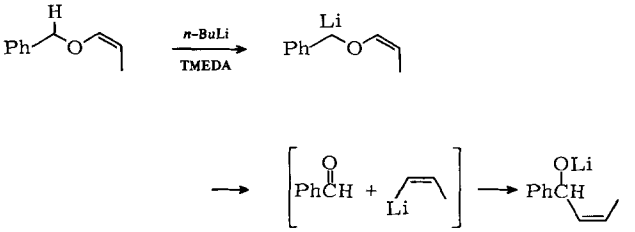
In this mechanism the rearrangement itself is depicted as occurring in a loose or solvent-separated ion pair. In contrast, the rearrangement of Grignard reagents[73a] is generally regarded as occurring by a concerted mechanism.

Scheme 2



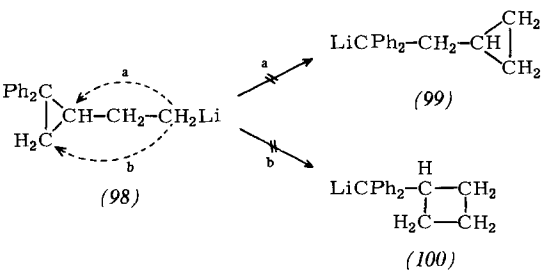


It has also been suggested[73b] for vinyl migrations in Wittig ether rearrangements that the initially formed lithium species cleaves to a vinyllithium derivative and a carbonyl compound, the two fragments then recombining to give the products.



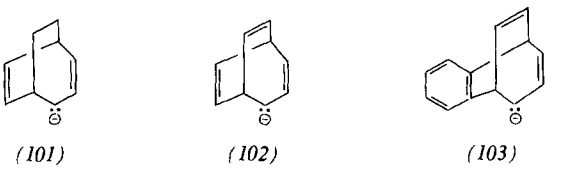
This mechanism accounts for the retention of geometry of the migrating vinyl group.

While cyclopropane rings sometimes behave somewhat like vinyl groups, it is notable that the organolithium compound *(98)* rearranged neither to *(99)* nor to *(100)*.

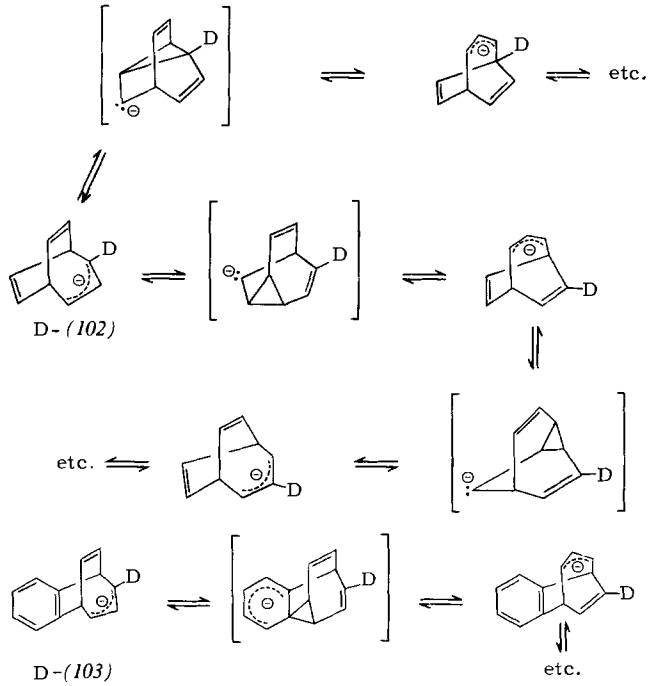


Instead, attempts[74] to force these rearrangements resulted in reaction of *(98)* with the solvent diethyl ether or tetrahydrofuran. What would much facilitate the study of such organoalkali compounds is a solvent which does not react with carbanions (cf. the "magic acid" of carbenium ion chemists).

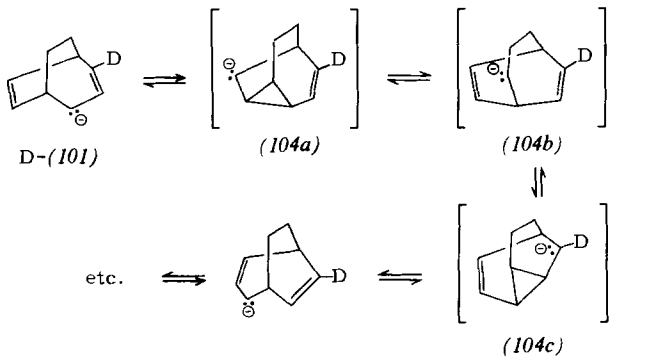
The bicyclic anions *(101)*, *(102)*, and *(103)* can be looked upon as homoallylic anions and hence in principle should



be able to undergo [1,2] vinyl migrations *via* cyclopropylmethyl intermediates. In fact, such rearrangements have been observed in suitably labeled derivatives of *(102)* and *(103)* but not of *(101)*. Thus *Grutzner* and *Winstein*[75] found that 2-deuteriobicyclo[3.2.2]nonatrienylyl anion D-*(102)* (as potassium salt) in an ethereal solvent underwent random scrambling of deuterium over all nine carbon atoms (four non-equivalent positions) of the anion with a half-life of 10 minutes at 28 °C. Similarly for D-*(103)* *Moncur*, *Grutzner*, and *Eisenstadt*[76] found that the deuterium label equilibrated over the seven carbons of the non-benzenoid moiety with a half-life of 1 hour at 32 °C; this seven-carbon scrambling

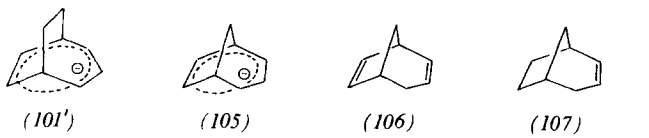


requires phenyl as well as vinyl migration. The deuterium-labeled bicyclo[3.2.2]nonadienyl anion D-*(101)* does *not* undergo analogous deuterium scrambling[76] evidently because this would require intervention of a series of unstable intermediates such as *(104a)*, *(104b)*, and *(104c)*.

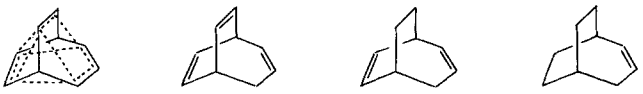


A cyclopropyl substituent evidently does not provide substantial stabilization[77] to an adjacent carbanionic center; the carbanions *(104a)* and *(104c)* and also the secondary carbanion *(104b)* are considerably less stable than the allylic anion *(101)*.

Indeed there is some evidence that the allylic anions *(101)*, *(102)*, and *(103)* are more stable than simple allylic anions. Thus anion *(101)* has been judged to be a bishomocyclopentadienyl anion[78] [see *(101')*] on the basis of both its NMR spectrum and its lifetime in ethereal solvents.



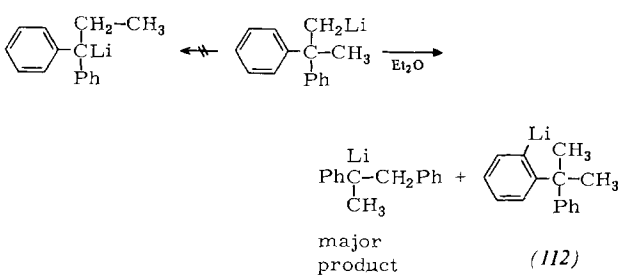
Similar arguments have been presented for the bishomoaromatic character of the lower homolog[79] *(105)*; the corresponding hydrocarbon *(106)* undergoes deuterium exchange with KO-*t*-Bu in dimethyl sulfoxide at 10^4 fold greater rate than *(107)* or cyclohexene. The anion *(102)* has been assigned the structure[75] *(108)* on the basis of its NMR spectrum. More detailed studies[78] upon *(108)* suggest that the major portion of the stabilization is due to bishomoaromatic stabilization (interaction between the allylic anion and *one* double bond); laticyclic interaction with the second double bond provides some 2.5 kcal/mol additional stabilization according



to studies upon the comparative lifetimes of *(101')* and *(108)* in tetrahydrofuran and 1,2-dimethoxyethane. A kinetic study[80] of detritiation of *(109)*, *(110)*, and *(111)* (all labeled with tritium at the allylic CH_2 group) by KO-*t*-Bu in dimethyl sulfoxide shows that *(109)* undergoes detritiation with an activation energy 4.0 ± 0.3 kcal/mol less than *(110)* while *(110)* has an activation energy > 5.6 kcal/mol less than that of *(111)*. While these studies are in agreement with structures such as *(101')* and *(108)* for the anions from detritiation, it was pointed out that the anion from *(111)* is formed less readily than anions from simple olefins and it was suggested that this anion was destabilized by interaction of the allylic moiety with the filled orbitals of the σ-framework. Since quantitative dissection of the observed reactivities into σ and π contributions is not resolved for the anions *(101)*, *(102)*, and *(103)* (if indeed it is resolvable), and because these anions and their related hydrocarbons have peculiar problems involving steric strain, the non-classical structures assigned to these anions must be accepted with some reservation. *Trimitsis* and *Tuncay*[81] have noted that the NMR spectra, in particular the sizable upfield shifts of *ca.* 1—2.5 ppm in the resonance of the protons directly attached to the remote carbon-carbon double bonds, do not necessarily imply that the anions in their ground states have the non-classical structures *(101')*, *(105)*, and *(108)*. It remains to be established whether the orbitals of these molecules, which have suitable symmetries and topologies for mixing and hence by molecular orbital theory must mix[82], do indeed undergo appreciable long range interaction.

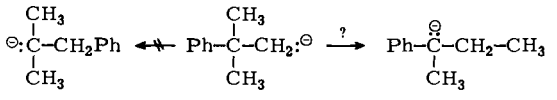
3.3. Migrations of Alkyl Groups and Hydrogen

As noted in Section 2, [1,2] migration of alkyl groups in simple carbanions is not expected to occur as a concerted process according to molecular orbital considerations. This negative expectation is in agreement with much useful synthetic



chemistry. It finds confirmation in the careful study of *Zimmerman* and *Zweig*[7] who reported no migration of methyl in rearrangement of 2,2-diphenylpropyllithium to 1-methyl-1,2-diphenylethyllithium; the by-product *(112)* arose by *ortho*-metalation. Also cleavage[7] of bis(2,2-diphenylpropyl)mercury with potassium gave [1,2] migration of phenyl but no [1,2] migration of methyl.

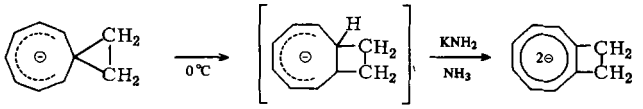
We considered that rearrangement of methyl in 2,2-diphenylpropyllithium might in principle occur but was masked by the more facile migration of phenyl. To test this postulate, reactions of neophyl chloride *(57)* with alkali metals have been studied. The corresponding 2-methyl-2-phenylpropyl anion (neophyl anion) *(113)* would not be expected to undergo phenyl migration since the product *(114)* would be a less stable tertiary anion; on the other hand, the product of methyl migration would be the more stable benzylic anion *(115)*. Reaction of neophyl chloride with lithium in THF



(114) *(113)* *(115)*

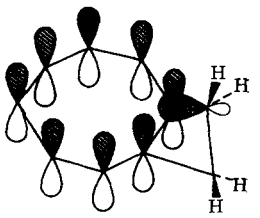
at −65 °C gave a product consisting of 93 % of neophyllithium *(59)* and 6 % of its rearrangement product 1,1-dimethyl-2-phenylethyllithium *(58)* (see Section 3.1); when the reaction mixture was warmed to 4 °C for 4 hours before carbonation, the reaction mixture contained less than 5 % (if any) of the 2-phenylbutane skeleton derived from *(115)*. Attempts to catalyze the rearrangement of neophyllithium with a large excess of *N,N,N',N'*-tetramethylethylenediamine in THF at −20 °C likewise did not give any appreciable products with methyl migration. Reaction of neophyl chloride with Cs-K and Cs-K-Na alloys in THF at −40 to −63 °C gave, upon carbonation, complex mixtures of products containing 1 to 4 % of an acid judged to be 2-methyl-2-phenylbutanoic acid [derived from *(115)*] according to its retention time in gas chromatographic analysis. Thus methyl migration is at most a minor reaction of carbanion *(113)*; additional work will be required to establish if any of the rearrangement product *(115)* arises by *direct intramolecular* methyl migration in *(113)*[83].

Are there any examples of concerted [1,2] migration of alkyl groups in carbanions? In carbanions containing only carbon and hydrogen such rearrangements at present are rare to non-existent. A possible example is provided by the rearrangement[84] of the spirocyclic anion *(116)* (with potas-



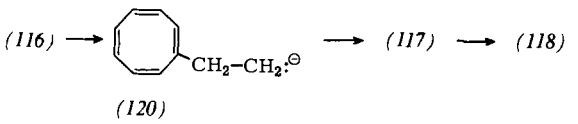
(116) *(117)* *(118)*

sium as counterion in liquid ammonia solution) to the anion *(118)* evidently by way of *(117)*. The rearrangement of *(116)* to *(117)* while resembling a [1,2] sigmatropic rearrangement may also be looked upon as a [1,8] rearrangement *via* a Hückel array of nine orbitals [see *(119)*] and 10 electrons, a transition state which is expected to be stable or aromatic by analogy with related [1,5]-alkyl shifts in cyclopentadienes[85]. As *Staley et al.*[84] noted, however, non-concerted rearrangements of *(116)* are not excluded by the available



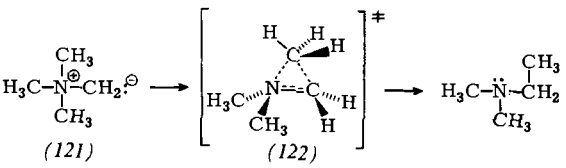
(119)

data. An attractive alternative involves a homoallyl anion *(120)*; in this case the initial rearrangement is but another example of the cyclopropylmethyl-homoallyl anion rearrangement of Section 3.2.



(120)

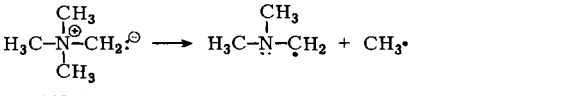
Are there any examples of concerted [1,2] migrations of alkyl groups in carbanions containing hetero atoms? We have answered this question in the affirmative for the Stevens rearrangement[37]; however the question continues to be one which is widely debated. Naive HMO calculations for the rearrangement of a simple ylide *(121)* [eq. (l)], with use of the parameters of *Zimmerman* and *Zweig*[7] but with the Coulomb integral



(121) *(122)* (l)

for nitrogen in *(121)* and *(122)* taken to be $\alpha + 1.5\beta$ rather than simply the value α for carbon, show that the transition state *(122)* is only 0.11β units higher in energy than *(121)*; this result, compared to a value of 1.33β for migration of a methyl group in the *n*-propyl anion (see Section 2), suggested to us[37] that migration of a methyl group in a simple ylide might be a facile concerted process. Qualitatively the difference between rearrangement of methyl in an all-carbon anion and in an anion such as *(121)* containing a heteroatom is that, if the heteroatom is sufficiently more electronegative than carbon, then the transition state will benefit by having more electron density on the more electronegative atom than will the reactant.

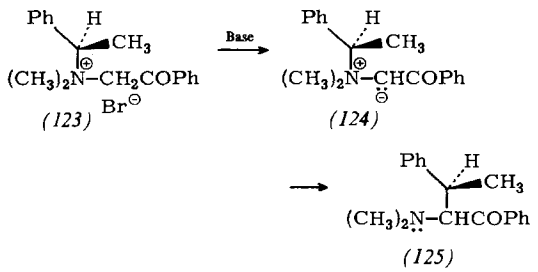
Dewar and *Ramsden*[86] have strengthened this argument by more complete calculations (MINDO/3) for the rearrangement of *(121)*. For rearrangement in the gas phase, the transition state *(122)* is calculated to lie only 4.1 kcal/mol above the reactant *(121)*, while the product *(123)* is 87 kcal/mol more stable than the reactant. Similar calculations also show, however, that in the gas phase the dissociation into radicals [eq. (m)] is exothermal by 10 kcal/mol and occurs without activation energy. The final product *(123)* could, therefore, be formed by combination of the resulting radicals. In practice



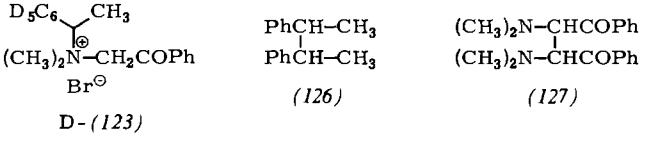
(121) (m)

Stevens rearrangements are carried out in solvents (water, alcohol, ethers) which will solvate polar molecules such as *(121)*. *Dewar* and *Ramsden* note that in the dissociation into radicals most of the solvation energy of *(121)* will be lost but that in formation of the cyclic transition state *(122)*, since this occurs early along the reaction coordinate, much solvation will persist; hence it was thought that the pericyclic path [eq. (l)] could be favored for rearrangement of the ylide in polar solvents. These calculations suggest to the author that the "forbidden" pericyclic mechanism and the radical dissociation mechanism should frequently be competitive processes with the net outcome dependent upon the detailed reaction conditions.

Experimental observations[87] appear to be in accord with this view. For example *Ollis, Closs, et al.*[88] have carefully re-investigated the rearrangement of the salt *(123)*. Treatment of *(123)* with aqueous sodium hydroxide at 0°C gave the



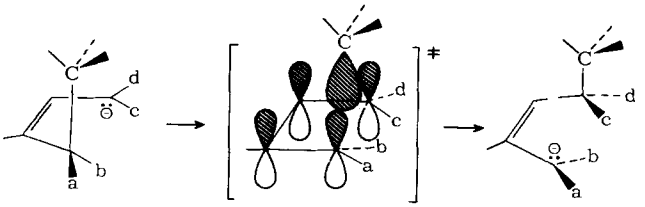
amine *(125)* with 99±1% net retention of configuration at the chiral center of the migrating α-phenylethyl group. The rearrangement was also shown under these conditions to be at least 99% intramolecular by mass spectral examination of the product from an equimolecular mixture of *(123)* (as racemic salt) and its racemic decadeuterio-derivative D-*(123)*. In contrast, in methanolic sodium methoxide at 55°C the salt *(123)* rearranges with 56% net retention and 44±2% racemization and gave intermolecular products to the extent



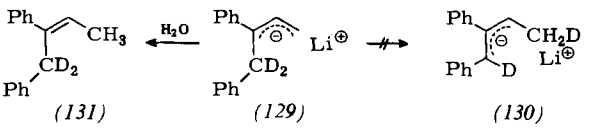
of about 20%. Under the latter conditions, but not under the former, the "escape" products *(126)* and *(127)* were formed, each in 6% yield of mixtures of the two possible diastereomers. A quantitative CIDNP study[89] of the rearrangement of the crystalline ylide *(124)* in $CDCl_3$ gave experimental enhancement factors of only some 25% of that calculated for the radical pair theory assuming freely diffusing radical pairs. These results are in agreement with rearrangement occurring by two competing mechanisms, one a radical pair process and the other a concerted pericyclic process, the latter being the dominant pathway under the conditions studied. Alternatively it may be argued that the entire process occurs by way of radical pairs but that the primary recombination rate is fast relative to the time for a radical to rotate within the pair or the time for a radical to diffuse from the solvent cage.

In a discussion of the related Wittig rearrangement of aralkyl alkyl ethers, *Garst* and *Smith*[90] point out that the distinction between a concerted process and one proceeding by a primary recombination of radicals within a solvent cage is rather ambiguous: one must decide arbitrarily on the degree of interaction between radicals, below which they would be classified as radical pairs and above which as an intermediate state or transition state for the concerted process. Rather than attempting to make such a distinction, *Garst* and *Smith* have suggested that such mechanisms be termed "radical-concerted."

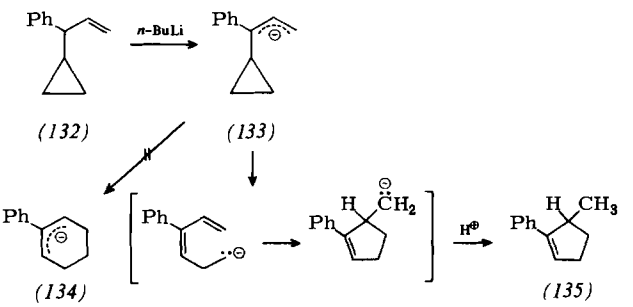
Are there any known examples of concerted [1,*n*] migration of alkyl groups in carbanions when *n* is larger than 2? As has been pointed out previously the rearrangement of *(116)*



may be an example of a [1,8] sigmatropic process. Suprafacial-suprafacial [1,4] sigmatropic rearrangements look especially promising and are allowed processes by orbital symmetry considerations[8]. Such migrations are seen to proceed by way of a transition state *(128)* which constitutes a Hückel array of five orbitals containing 6 electrons and is therefore expected to be "aromatic." *Magid* and *Wilson*[91] noted that the anion *(129)* failed to give *(130)* *via* [1,4] migration of deuterium when the red hexane/THF solution was refluxed overnight; hydrolysis gave *(131)* with an unchanged molecular



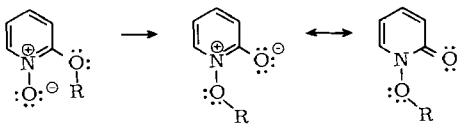
skeleton. The cyclopropyl compound *(132)*, upon reaction with *n*-butyllithium in hexane/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine followed by heating at 60°C for one hour before hydrolysis, gave *(135)*[91], probably by rearrangement to a homoallyl anion as shown, rather than [1,4] migration of



methylene to give *(134)*. These failures show that [1,4] migration is not a ready process in allylic anions. The rearrangement of *(133)* to *(134)*, while it would involve relief of ring strain, would also require loss of delocalization energy [the phenyl group in *(134)* is located on a carbon which is at a nodal position in the highest filled molecular orbital of the allylic anion]. Also in the transition state [see *(128)*] for [1,4] migra-

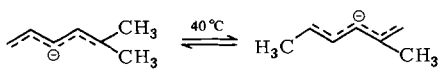
tion, steric interference between groups b and c would be expected to inhibit bringing the ends of the diene moiety close enough for bridging by the migrating group. Perhaps it is the absence of such groups which facilitates rearrangement of 2-alkoxypyridine *N*-oxides along with other beneficial effects of electronegative oxygen atoms.

Schöllkopf and *Hoppe*[92] in a systematic study of the rearrangement of 2-alkoxypyridine *N*-oxides *(136)* to *N*-alkoxy-2-pyridones *(137)* find that the rearrangement is first order and



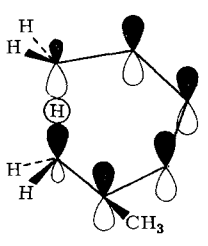
(136) *(137)*

occurs with apparently complete retention of configuration of the migrating group (R = CHDPh). The rate difference for migration of common alkyl groups (methyl, ethyl, isopropyl, neopentyl) is small (less than ninefold). Unsaturation in the migrating groups facilitates migration; benzyl, allyl, and 2,4-hexadienyl migrate some three, eleven, and one-thousand fold more readily than methyl but the Hammett ρ value for migrating benzyl groups is only *ca.* −0.3. Allyl, propargyl, and 2,4-hexadienyl migrate without "allyl inversion" and cyclopropylmethyl migrates without skeletal rearrangement. The enthalpy of activation is small (5 to 14 kcal/mol) while the entropy of activation is very negative (−43 to −62 cal K^{-1} mol^{-1}). As *Schöllkopf* and *Hoppe* note, these facts agree well with migration of the group R of *(136)* by a concerted suprafacial-suprafacial [1,4] process [see transition state *(128)*]. On the other hand when R is benzhydryl, the product of rearrangement shows a CIDNP signal; rearrangement evidently occurs by a radical-pair process. Some anionic rearrangements of allylammonium salts[93] and allyl ethers[94] also occurs with [1,4] migration of alkyl groups but the mechanisms of these rearrangements have not been clarified.

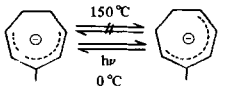


(138) *(139)*

Thermal isomerizations such as the reaction *(138)* ⇌ *(139)*, involving concerted antarafacial [1,6] migrations of hydrogen, are believed to occur in pentadienyl anions *via* an intramolecular process according to *Bates et al.*[95]. The transition state *(140)* for the proton migration of the lithium salt of *(138)* in THF/hexane evidently is preceded and followed by geometrical isomerization. This transition state is a Möbius array of orbitals (one sign inversion in the basis set) which is popu-



(140)



(141) *(142)*

lated by 8 electrons and hence is expected to be an allowed (or aromatic) transition state[15]. In contrast, the related thermal rearrangement of *(141)* to *(142)*, if a concerted intramolecular process, is constrained so that only a forbidden suprafacial [1,6] proton migration is sterically feasible. In agreement anion *(141)* did not rearrange to *(142)* (or *vice versa*) when heated to 150 °C for 30 minutes; however, the suprafacial [1,6] hydrogen migration occurred upon irradiation at 0 °C with a high-pressure mercury lamp in a quartz apparatus as expected from the theory of conservation of orbital symmetry[8].

3.4. Migration of the Benzyl Group in Competition with Phenyl

Reaction of 1-chloro-2,2,3-triphenylpropane with lithium in THF at −65 °C gives, as expected, 2,2,3-triphenylpropyllithium *(143)*. When the latter is warmed to 0 °C, rearrangement to 1,1,3-triphenylpropyllithium *(144)* occurs readily[96].

$$PhCH_2{-}CPh_2{-}CH_2Cl \xrightarrow{Li} \underset{(143)}{PhCH_2{-}CPh_2{-}CH_2Li}$$

$$\xrightarrow{0\,^\circ C} \underset{(144)}{LiCPh_2{-}CH_2{-}CH_2Ph}$$

This rearrangement has the appearance of a concerted [1,2] sigmatropic migration of the benzyl group; however, experiments[37,97] soon showed that this was not the case. Thus rearrangement of *(143)* in presence of [α-^{14}C]-benzyllithium gave *(144)* labeled with carbon-14. A likely mechanism for this incorporation of external benzyllithium is *via* an elimination-readdition mechanism [eq. (n)]. The rearrangement was

$$\underset{(143)}{PhCH_2{-}CPh_2{-}CH_2Li} \rightarrow PhCH_2Li + Ph_2C{=}CH_2$$

$$\xrightarrow{Ph\,{}^*CH_2Li} \underset{^{14}C\text{-}(144)}{LiCPh_2{-}CH_2{-}{}^*CH_2Ph} \qquad (n)$$

shown to be irreversible; the benzyllithium which became incorporated in the product *(144)* had the same activity as the benzyllithium in the bulk of the solution at the time of the addition. Alternatively a fragmentation of *(143)* into benzyl radical and diphenylethylene radical anion could also account for the results if lithium atom exchange between benzyllithium and benzyl radical is assumed to be rapid. We have always favored the elimination-addition mechanism since in MO theory diphenylethylene radical anion has in its highest occupied molecular orbital (HOMO) an electron which is antibonding whereas benzyl anion has in its HOMO nonbonding electrons. (In contrast, in the Wittig and Stevens rearrangements the corresponding radical anion is stabilized by electronegative oxygen and nitrogen atoms, respectively.) The intermediate diphenylethylene in rearrangement of *(143)* could also be intercepted by isopropyllithium[37].

In opposition to the above results with lithium, reaction[35] of 1-chloro-2,2,3-triphenylpropane with cesium in THF at 65 °C gives organometallic products containing 96 % of [1,2] migration of phenyl rather than benzyl [eq. (o)].

$$PhCH_2{-}CPh_2{-}CH_2Cl \xrightarrow{Cs} [PhCH_2{-}CPh_2{-}CH_2Cs] \longrightarrow PhCH_2{-}\overset{Ph}{\overset{|}{C}}{-}CH_2Ph \quad (Cs^{\oplus}) \qquad (o)$$

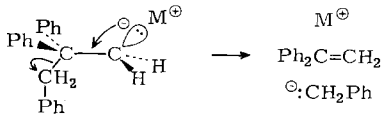
A more detailed study of the cation effect was conveniently made by reaction[98] of the unrearranged organolithium compound *(143)* with alkali metal alkoxides in THF according to the metathetical reaction of eq. (p). While the lithium compound *(143)* does not rearrange at an appreciable rate in

$$\underset{(143)}{PhCH_2{-}CPh_2{-}CH_2Li} + MO\text{-}t\text{-}Bu \longrightarrow PhCH_2{-}CPh_2{-}CH_2M + LiO\text{-}t\text{-}Bu \qquad (p)$$

THF at −75 °C, addition of sodium *tert*-butoxide or better potassium and cesium *tert*-butoxides under the same conditions effected ready rearrangement. The rearrangement product with sodium *tert*-butoxide was entirely that of benzyl migration, while with potassium and cesium *tert*-butoxide the ratio of benzyl to phenyl migration was 63:37 and 26:74 respectively. If, however, the potassium and cesium *tert*-butoxides were complexed with 18-crown-6 prior to addition to the lithium reagent, the only rearrangement product was that from benzyl migration.

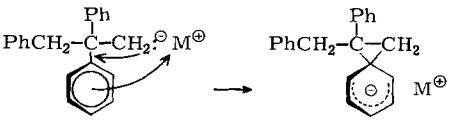
These and other experiments[35] reveal that the following compounds undergo reaction almost exclusively by benzyl migration: 2,2,3-triphenylpropyllithium and -sodium in THF at 0 °C and −75 °C, respectively; 2,2,3-triphenylpropylpotassium and -cesium as 18-crown-6 complexes in THF at −75 °C. The following undergo rearrangement almost exclusively by phenyl migration: 2,2,3-triphenylpropyllithium in diethyl ether at 35 °C; 2,2,3-triphenylpropylpotassium and -cesium in THF at 65 °C. Stated otherwise, benzyl migration is favored by low temperatures, good solvents for solvating cations, coordination of cations by 18-crown-6, and small alkali metal cations; phenyl migration is favored by high temperatures, poorly solvating solvents, absence of good ligands, and large alkali metal cations. The conditions which favor benzyl migration favor loose or separated ion pairs, while those which favor phenyl migration favor tight or contact ion pairs[99]. In terms of the likely mechanisms for migration, it appears that benzyl cleavage [see eq. (n)] occurs in a transition state resembling a loose ion pair while phenyl migration (see Section 3.1) occurs in a transition state resembling a tight ion pair.

These results may be rationalized[35] on the basis that benzyl cleavage occurs in an *anti-periplanar* conformation [see *(145)*] which gives rise to a delocalized benzyl anion separated from the counter cation by a molecule of diphenylethylene. The negative charge is greatly separated from the cation in the



(145)

transition state for this reaction; the electrostatic work required for such charge separation is greatly reduced by solvation of the cation as in a loose ion pair. In contrast, for the transition state [see *(146)*] leading to the spiro anion *(147)*, the alkali metal cation in the tight ion pair may accompany the anionic center during bridging such that no great charge separation is necessary at anytime for the cyclization.

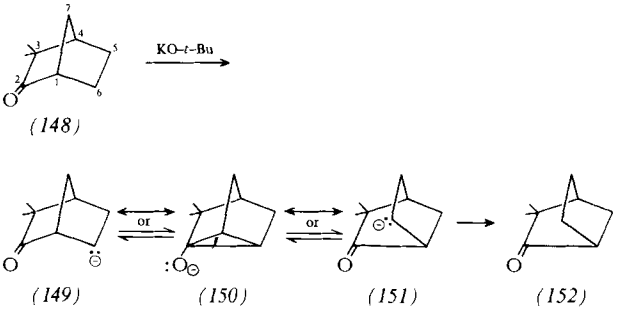


(146) *(147)*

Hence phenyl migration does not benefit as much from solvation of the cation as does benzyl cleavage. Some related solvent effects were observed by *Biellmann* and *Schmitt*[100] in studies of the Stevens rearrangement in competition with the Sommelet-Hauser rearrangement.

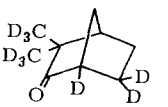
3.5. Migration of Carbonyl, Alkoxycarbonyl, *etc.*

Nickon et al.[101] established that optically active camphenilone *(148)* when heated strongly (*ca.* 185 °C) with potassium *tert*-butoxide in *tert*-butyl alcohol undergoes racemization, evidently by the reaction shown.



(148) *(149)* *(150)* *(151)* *(152)*

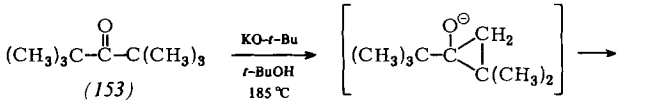
When the reaction was conducted in *t*-BuOD the percentage of racemization and the total percentage of molecules containing deuterium were the same within experimental error. The conclusion was that the intermediate "homoenolate" either had a symmetrical structure [resonance hybrid of the canonical structures *(149)*, *(150)*, and *(151)*] or else if unsymmetrical like *(149)* it rearranged to its enantiomer *(151)* faster than it reverted to ketone. Since the rate of deuterium exchange equals the rate of racemization, the homoenolate ion is the most stable anion which can be formed from ionization of ketone. This fact implies that the homoenolate ion must receive appreciable stabilization by homoconjugation [some resonance interaction between *(149)* and *(150)*] since if only inductive effects were involved the anion at the position (C-1) *alpha* to the carbonyl group would be most acidic (note that mesomeric stabilization of this enolate ion is inhibited by approximate orthogonality of orbitals). Upon prolonged reaction with potassium *tert*-butoxide in *t*-BuOD at 185 °C or better at 250 °C, camphenilone *(148)* exchanged up to nine hydrogens per molecule, the completely deuterated product being D-*(148)* (and enantiomer).



D-*(148)*

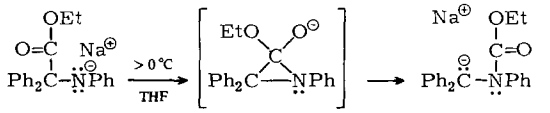
This experiment shows that the anion at the bridgehead position C-1 is not much less stable than the homoenolate ion; also ionization of both methyl groups gives homoenolate ions. In contrast, the proton at C-7 and the remote protons at C-4 and C-5 are not ionized. This positional specificity is understandable if the carbanionic center must undergo some orbital interaction with the carbonyl group for stabilization. That *both* protons on C-6 are exchanged shows that protonation of the enolate is not entirely stereospecific even though >94% of the homoenolate [*(149)—(151)*] is thought to be protonated at the *exo* position (the side more remote from the carbonyl).

The racemization of camphenilone *(148)* involves an overall [1,2] migration of the carbonyl group. *Freeman* and *Plonka*[102] generated homoenolate ions by indirect methods and showed that the expected migration of carbonyl group occurred. Recently *Rampersad* and *Stothers*[103] have shown that ionization of the β-hydrogens of di-*tert*-butyl ketone *(153)* and 5,5,7,7-tetramethylundecan-6-one does indeed give skeletal rearrangement.



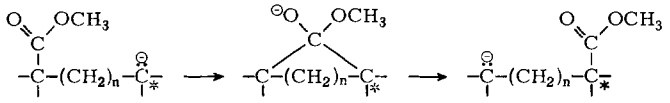
(153) *(154)*

Brooke and *Rutherford*[104] discovered an example of [1,3] migration of a trifluoroacetyl group from nitrogen to carbon. *Smith* and *Simpson*[105] reported an example of [1,2] migration of an ethoxycarbonyl from carbon to nitrogen [*(155)→(156)*]. *Acheson*[106] has suggested that in general



(155) *(156)*

[1,2], [1,3], [1,4], and [1,5] migration of alkoxycarbonyl groups should occur in carbanions such as *(157)→(158)* and cites several possible examples, which, however have not been studied in mechanistic detail. Related rearrangements

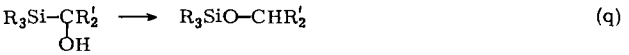


(157) *(158)*

of anions such as of the *N,N*-dimethylthioamide group[107] have also been reported. All of these rearrangements have striking similarity to the migration of vinyl groups (Section 3.2) and can be viewed as related to intramolecular aldol condensations.

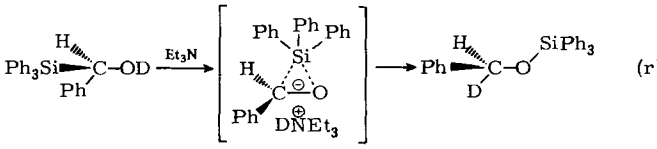
3.6. Migration of Silyl, Germyl, and Related Groups

While [1,2] sigmatropic suprafacial shifts of alkyl groups in carbanions are forbidden by orbital symmetry (Section 2) and occur with difficulty, if at all, except when electronegative hetero atoms are present (Section 3.3), similar migrations of silyl groups may occur without symmetry restrictions through a pentacoordinate transition state (or intermediate). An early example was the Brook rearrangement[108] of silylmethanols [eq. (q)] which is promoted by traces of sodium-po-



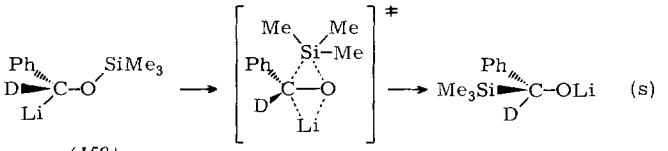
(q)

tassium alloy or bases such as pyridine or triethylamine. By use of optically active compounds containing a chiral silicon center, it was shown that the silyl group migrated with retention of configuration. Studies with an asymmetric carbon center[108, 109] showed that a highly stereospecific inversion of configuration occurred at the chiral carbon center during rearrangement [see eq. (r)]. The reverse rearrangement is pro-



(r)

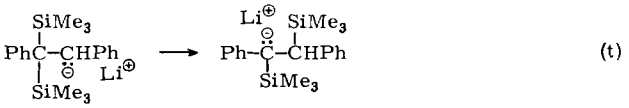
moted by metalation at the benzyl carbon atom with excess *tert*-butyllithium in THF/pentane at −50 °C followed by decomposition with excess acetic acid; again the migration occurs with highly stereospecific inversion[110], evidently according to eq. (s). The abstraction of the proton by *tert*-butyllithium to give *(159)* and the movement of silicon into the bridging position *(160)* may be almost concerted.



(159) *(160)*

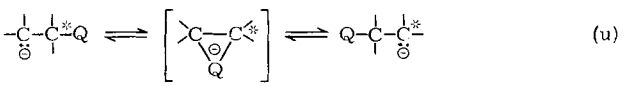
(s)

Many analogous [1,2] and also [1,4] migrations of organosilyl groups to and from various hetero atoms have been discovered by *West et al.*[111]. Similar [1,2], [1,3], and [1,4] shifts of organosilyl groups from carbon to a carbanionic center [*e.g.*, eq. (t)] have been reported by *Eisch* and *Tsai*[112].



(t)

Germanium[110, 113] and phosphonium[114] compounds have been found to undergo related anionic rearrangements with migration of germanium and phosphorus centers. As has been pointed out previously[39], for concerted rearrangements of the type shown in eq. (u), the group Q needs to be unsaturated (vinyl, carbonyl, aryl) or to possess "unsaturated" character because of the presence of vacant d or p

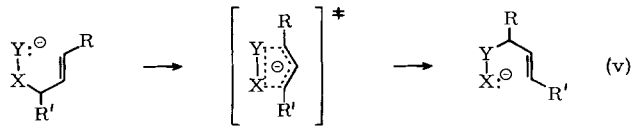


(u)

orbitals on the atom Q. It seems likely that many additional examples of such rearrangements will be reported in the future.

4. [2,3] Sigmatropic Rearrangements of Carbanions; Migration of Allyl Groups

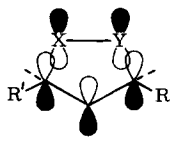
The [2,3] sigmatropic rearrangement of ylides and related anionic species [*(161)* → *(163)*] is a process of great facility and widespread occurrence[87, 115]. That this rearrangement



(v)

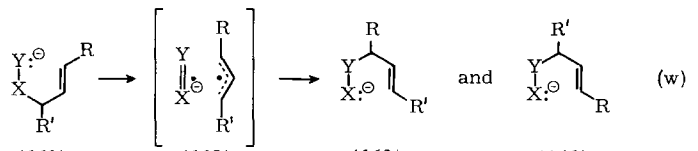
(161) *(162)* *(163)*

involves an allylic inversion was clearly demonstrated by *Schöllkopf* and *Fellenberger*[116] for allyl migration in the anions of fluorenyl allyl ethers. That the rearrangement occurs suprafacially for both the X-Y and the allylic moiety was demonstrated by *Baldwin* and *Patrick*[115] in studies upon rearrangement of the anion of the benzyl ether of (*S*)-*trans*-3-penten-2-ol. The transition state *(162)* for this concerted rearrangement is shown in terms of the basis set of atomic orbitals in *(164)*. It is notable that this array of orbitals constitutes a Hückel system and, since it contains six π-electrons, is expected to be a stable or "aromatic" transition state.



(164)

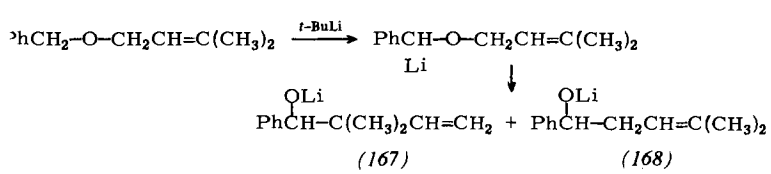
While the concerted mechanism constitutes the major path in rearrangement of allyl ether anions, and related species, *Baldwin et al.*[117] have suggested that a duality of mechanism exists with minor products being formed with only partial allylic inversion by a non-concerted radical dissociation-recombination process [*(161)* → *(163)* and *(166)*]. The extent of the radical dissociation process increases with temperature.



(w)

(161) *(165)* *(163)* *(166)*

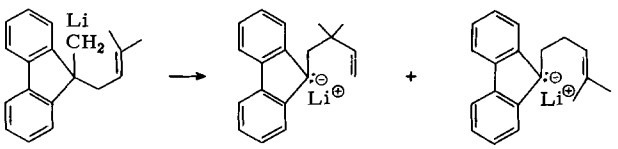
Thus benzyl 3-methyl-2-butenyl ether with *tert*-butyllithium gives[117] a 95:5 mixture of *(167)* and *(168)* at 25°C and a 98:2 mixture at −10°C. While the rearrangement of *(161)* to *(163)* and *(166)* has been depicted as giving *trans* products, lesser quantities of *cis*-products are also formed[115], presumably by both mechanisms [eqs. (v) and (w)].



(167) *(168)*

Other examples of the general rearrangement of *(161)* to *(163)* [and sometimes *(166)*] are allyl migration in anions of thio ethers[118], in allylic disulfides[119], in sulfur[120] and nitrogen ylides[121], in *N*-ammonio-amidates[122], in amine oxides[123], and in diazenes[124]. The Sommelet-Hauser rearrangement may be looked upon as a specialized example of the same general process. These rearrangements are closely akin to the Cope and Claisen rearrangements. Are any [2,3] sigmatropic rearrangements known in anions containing only carbon and hydrogen? Two cases have, in fact, been studied.

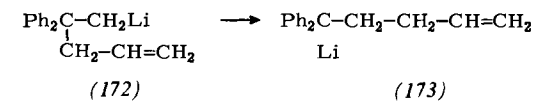
Baldwin and *Urban*[125] observed that [9-(3-methyl-2-butenyl)-9-fluorenyl]methyllithium *(169)* rearranges in THF to give predominantly the lithium compound *(170)* at −20°C



(169) *(170)* *(171)*

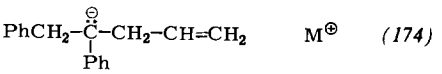
along with *(171)* which was formed in increasing amounts as the temperature was raised. Their interpretation was that *(170)* was formed by an anionic [2,3] sigmatropic rearrangement [eq. (v)] while *(171)* (and an unknown amount of *(170)*) resulted from a radical dissociation-recombination process [eq. (w)].

In related work[126] 2,2-diphenyl-4-pentenyllithium *(172)* was observed to rearrange in THF at −50 to 0°C to give chiefly 1,1-diphenyl-4-pentyllithium *(173)*. With [3-^{14}C]-2,2-diphenyl-4-pentenyllithium, carbon-14 was found in *(173)*



(172) *(173)*

either at the terminal C-5 position (allylic inversion) or scrambled at positions C-3 and C-5. The amount of scrambling increased with increasing temperature, being some 37% at −50°C and 67% at *ca.* 0°C. Potassium and cesium *tert*-butoxides with *(172)* in THF at −75°C induced ready rearrangement to give chiefly 1-benzyl-1-phenyl-3-butenyl anion *(174)*, which is the product of [1,2] migration of phenyl. When, however, the potassium *tert*-butoxide was complexed with 18-crown-6 prior to addition to *(172)* in THF at −75°C,

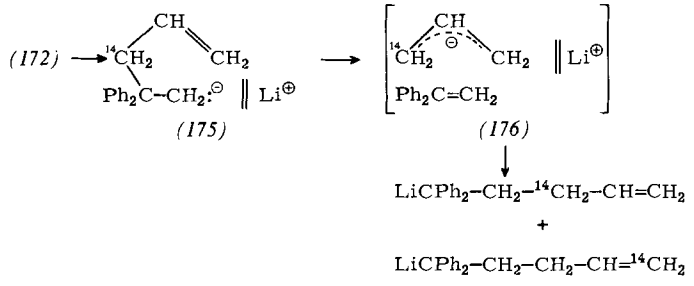


(174)

the chief product was 1,1-diphenyl-4-pentenyl anion which was formed with complete inversion of the allyl group according to a tracer study with carbon-14. These results are interpreted to mean that allyl migration occurs in a highly solvated transition state, probably in a loose ion pair either by a [2,3] sigmatropic process (with allylic inversion), favored by low temperatures, or by a dissociation-recombination mechanism (with scrambling of the allylic label); on the other hand, phenyl migration occurs in a more weakly solvated

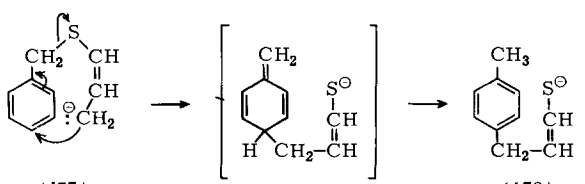
transition state, likely in a tight ion pair, by a [1,2] sigmatropic process (see Section 3.4).

The details of the dissociation-recombination mechanism are unclear. In an experiment in which the lithium compound *(172)* was mixed with [^{14}C]-allyllithium prior to warming in THF, from −75 to 0 °C to effect rearrangement, the resulting product from allyl migration had picked up only 14% of the maximum possible radioactivity from the allyllithium in the surrounding solution. Yet under these conditions, 67% allylic scrambling and 33% inversion occurs. One possible mechanism is by elimination of allyllithium from a loose ion pair *(175)* derived from *(172)*. Evidently the eliminated



allyllithium is formed initially as a loose ion pair which collapses to ordinary allyllithium at a rate of about 14/67th or 21% of that at which addition occurs to diphenylethylene. The rate of collapse of the loose ion pair is expected to be very fast and hence the rate of addition of the loose ion pair to diphenylethylene must be somewhat faster. In contrast ordinary allyllithium, which evidently exists in THF as a tight ion pair, in which the carbon-metal bond is partially localized or covalent, adds to diphenylethylene comparatively slowly. If the collapse of the loose ion pair of allyllithium occurs nearly at the diffusion-controlled rate, then the intermediates *(176)* need to be described as existing within a solvent cage. The loose ion pair must then add to diphenylethylene at about the diffusion-controlled rate, a process which is perhaps facilitated by having the diphenylethylene as a ligand of the lithium cation. The mechanistic complexities here are somewhat analogous to those described (see Section 3.3) for the Stevens rearrangement; indeed a radical dissociation process [eq. (w)] is not excluded by the available data.

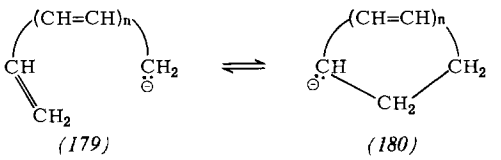
Are there any sigmatropic rearrangements of carbanions of order higher than [2,3]? The question probably should be answered in the affirmative since *Fráter* and *Schmid*[127] have reported [5,5] sigmatropic shifts to occur with allylic inversion in rearrangements of 2,4-pentadienyl phenyl ethers. Indeed, *Biellmann* and *Ducep*[118b] have reported the isolation of *(178)* (as methyl thioether) among other rearrangement



products from reaction of benzyl allyl sulfide with *n*-butyllithium. Evidently *(178)* results from a [4,5] sigmatropic rearrangement of *(177)* (*via* a transition state consisting of a Hückel array of nine orbitals containing 10 electrons); however, other mechanisms have not been excluded.

5. Electrocyclic Reactions of Carbanions

The migration of phenyl and vinyl groups in carbanions has been described as involving cyclization followed by ring opening (see Sections 3.1 and 3.2); however, the process under discussion in the present section refers to cyclization of fully conjugated systems and the converse process [*(179)*⇌*(180)*]. Examples are now known for the cases $n=0$ (ring opening), $n=1$ (ring opening and ring closure), and $n=2$ (ring closure).



In most cases so far tested, the geometrical modes of ring opening and closure are in accord with predictions[8] from orbital symmetry ($n=0$ or 2, conrotatory; $n=1$, disrotatory). These reactions have been discussed in detail elsewhere[128].

6. Conclusions

The question of whether or not carbanions undergo molecular rearrangement must be answered in the affirmative even for anions containing only carbon and hydrogen as work of the last twenty years from diverse laboratories has now made abundantly clear.

Most skeletal rearrangements of carbanions belong to the general class of *intramolecular* rearrangements. Such reactions have always fascinated chemists, in part because they represent organic reactions at the simplest possible level of complexity. For intramolecular reactions, chemists no longer need to be concerned about the ordinary requirement of molecular collisions to bring molecules into proper contact. Instead organoalkali compounds must undergo suitable solvation and conformational changes; however, for rearrangement *via* cyclic transition states of small to medium ring size the number of possible conformations is limited and the choice between them can generally be made from stereochemical studies. Hence intramolecular rearrangements frequently occur in transition states of known geometry. Concerted intramolecular rearrangements necessarily involve cyclic transition states. Cyclic structures involving conjugated systems have unique properties, as first recognized by *Kekulé* for benzene. The application of quantum mechanics to the study of such cyclic molecules and related transition states has enjoyed considerable success and nowhere is this more evident than in the study of rearrangements of carbanions.

More complex are rearrangements of organoalkali compounds which do not take place by intramolecular paths. Interestingly many of these appear to be at the borderline between concerted and non-concerted processes; here even the distinction between homolytic and heterolytic cleavage may be blurred.

Chemists should note, however, that simple molecular orbital theory omits the role of the counterion and the solvent. By variation of the alkali metal, the temperature, the ligands of the metal cation and/or the solvent, the chemist is able to exert considerable control over the rate of rearrangement, the relative migratory aptitude of groups, and the mechanism of rearrangement. That carbanion rearrangements do not occur in acyclic saturated anions is of considerable importance in synthetic chemistry. The rapidity and complexity of rearrangements of carbenium ions has severely limited their utility in synthesis.

It is the author's hope that this review may help make syntheses *via* organoalkali compounds more successful by pointing out the general conditions needed to effect rearrangement and the type of rearrangement which may be encountered. Occasionally rearrangement itself may produce structures which are not readily available by other pathways. Surely future workers will uncover yet unsuspected rearrangements of organoalkali compounds.

The author is pleased to acknowledge the many contributions of current and former students and research associates who did most of the work ascribable to the author's laboratory. Financial support from the National Science Foundation for all the recent work is gratefully acknowledged.

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[6] For the details of this method see standard texts such as *H. E. Zimmerman*, Quantum Mechanics for Organic Chemists, Academic Press, New York 1975; *E. Heilbronner, H. Bock*, Das HMO-Modell und seine Anwendung, Verlag Chemie, Weinheim 1968.
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Mechanistic and Preparative Aspects of Vinyl Cation Chemistry

By Michael Hanack[*]

Compelling evidence for the intermediacy of vinyl cations has accumulated in recent years. Vinyl cations can be generated by electrophilic additions to alkynes and allenes, and on participation of such functions in solvolysis reactions. Heterolysis of vinyl compounds likewise affords vinyl cations. Syntheses of substituted indenes, cyclobutanones, and cyclopropyl ketones illustrate preparative applications.

1. Introduction

Few areas of organic chemistry have been studied so intensively over a period of 75 years as has the chemistry of carbenium ions. The term carbenium ion was long applied only to those intermediates in which the positively charged carbon atom is linked to three substituents (trisubstituted or saturated carbenium ions) *(1)*.

(1) $-\overset{|}{\underset{|}{C}}-\overset{\oplus}{C}$ $\quad$ $>C=\overset{\oplus}{C}-$ *(2)*

Only comparatively recently have disubstituted carbenium ions, of which the vinyl cation *(2)* is an important representative, been studied in detail; thus in 1969 *W. M. Jones* was at last able to write: "Vinyl cations have finally become acceptable members of the reactive intermediate community"[1].

Apart from vinyl cations, acylium *(3)* and nitrilium ions *(4)* also number among the disubstituted carbenium ions. A further disubstituted carbenium ion, *i.e.* the phenyl cation *(5)*, has so far been unequivocally detected in only few reactions.

$-\overset{\oplus}{C}=\ddot{O} \longleftrightarrow -C\equiv\overset{\oplus}{O}:$ $\qquad$ $-\overset{\oplus}{C}=\ddot{N}-R \longleftrightarrow -C\equiv\overset{\oplus}{N}-R$

(3) $\qquad$ *(4)*

(5)  $\qquad$ $-C\equiv\overset{\oplus}{C}$ *(6)*

The monosubstituted ethynyl cation *(6)* corresponds to the disubstituted vinyl cation *(2)*. Calculations have shown *(6)* to have a particularly high energy; however, experimental evidence has yet to be obtained for its existence[2, 3].

Textbooks often state that vinyl cations *(2)* occur only rarely as intermediates owing to their low stability, but recent studies have revealed a large number of reactions proceeding *via* vinyl cations. In some reactions, vinyl cations qualitatively resemble saturated carbenium ions.

One of the reasons for rejecting vinyl cations as intermediates was considered to be the modest reactivity of vinyl halides in solvolysis reactions, *i.e.* it appeared unlikely that these species could react *via* an S_N1 mechanism. Although it was generally accepted that, *e.g.* electrophilic additions to a double and a triple bond should proceed according to the same mechanism, vinyl cations were formulated only reluctantly as intermediates in electrophilic additions.

The chemistry of vinyl cations has now come very much to the fore. This is partly a result of more accurate mechanistic studies on electrophilic additions to acetylenes and allenes. However, the observation that vinyl cations can also be generated under certain conditions by simple solvolysis reactions led to a breakthrough in the chemistry of these intermediates. Subsequent developments in vinyl cation chemistry also led to interesting preparative applications.

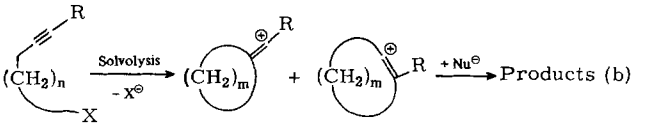
Direct detection of vinyl cations by ^{1}H- and ^{13}C-NMR spectroscopy has also been attempted[4].

Vinyl cations occur as intermediates in electrophilic additions and in solvolysis reactions which proceed with neighboring group participation. These include electrophilic additions to CC triple bonds [eq. (a)],

$$R-C\equiv C-R' + E^{\oplus} \longrightarrow \underset{R}{\overset{E}{}}C=\overset{\oplus}{C}-R' \xrightarrow{+Nu^{\ominus}} \text{Products} \qquad \text{(a)}$$

$E^{\oplus}$ = e.g. $H^{\oplus}$, carbenium ions; $Nu^{\ominus}$ = e.g. halide

solvolysis reactions involving these bonds [eq. (b)],

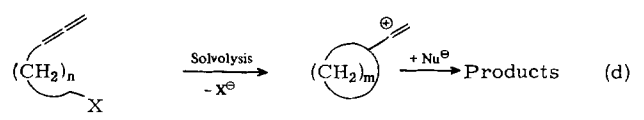


R = H, Alkyl, Aryl; $X^{\ominus}$ = Halide, Sulfonate

electrophilic additions to allenes [eq. (c)],

$$>C=C=C< + E^{\oplus} \longrightarrow >C=\overset{\oplus}{C}-\underset{E}{C}< \longrightarrow \text{Products} \qquad \text{(c)}$$

and solvolysis reactions involving this group [eq. (d)].



Heterolysis of vinyl compounds [eq. (e)] likewise leads to vinyl cations. Among the special reactions, mention should be made of photochemical processes.

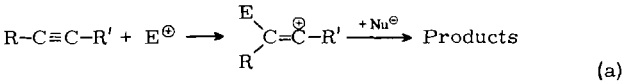
$$>C=\underset{X}{C}< \longrightarrow >C=\overset{\oplus}{C}- + X^{\ominus} \qquad \text{(e)}$$

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In the present article, examples of these reactions for generating vinyl cations will be considered from a present-day mechanistic vantage point and preparative applications will be described. Comprehensive surveys of vinyl cation chemistry have been published[5], and reviews have appeared on such detailed aspects as the chemistry of stabilized vinyl cations[6] or solvolyses of α-arylvinyl derivatives[7].

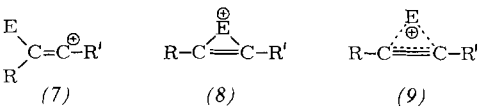
2. Electrophilic Additions and Solvolyses Proceeding with Neighboring Group Participation

2.1. Electrophilic Additions to CC Triple Bonds



$E^{\oplus}$ = e.g. $H^{\oplus}$, carbenium ions; $Nu^{\ominus}$ = e.g. halide (a)

Like electrophilic additions to CC double bonds, additions to CC triple bonds can also proceed stepwise, as shown in eq. (a) (Ad_E2 mechanism). The linear vinyl cation *(7)* formed transiently in the slow step is attacked from both sides by nucleophile $Nu^{\ominus}$, yielding the products in a non-stereospecific reaction. This simple addition scheme, however, is of limited validity and applies only to simple acetylenes[8,9,17]. Subsequent studies have shown that the direction of nucleophilic attack on the vinyl cation *(7)* depends upon the relative size and upon the electronic character of the β-substituents R and E[10–12]. Owing to ion-pair formation on addition, the *cis* isomer can predominate. The intermediate cation is not necessarily an open vinyl cation. Depending upon the structure of the acetylene and the attacking electrophile, an "onium" cation *(8)* (σ bridged) or a π-bridged cation *(9)* may also act as intermediate. Attack of *(9)* by nucleophile would preferentially yield the *trans* product.—Electrophilic addition to acetylenes may also follow an Ad_E3 mechanism, instead of the Ad_E2 mechanism.

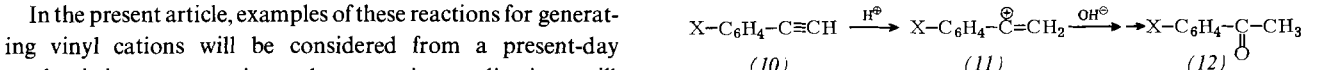


(7) *(8)* *(9)*

The most thoroughly studied electrophile is the proton; however, other species such as carbenium ions may also be involved. Among all electrophilic additions to alkynes, addition of $H^{\oplus}$ shows the greatest variation; its mechanism is a function of the reaction conditions. In the case of highly polar, strongly acidic, but only weakly nucleophilic acids such as trifluoroacetic acid, a vinyl cation is formed preferentially as intermediate; with less polar and more strongly nucleophilic reactants, *e.g.* acetic acid, other addition mechanisms prevail[5c]. Arylacetylenes can react *via* different mechanisms from alkylacetylenes. Some examples are presented in Section 2.1.1.

2.1.1. Addition of Acids to Aryl- and Alkyl-acetylenes

Acid-catalyzed hydration of variously substituted arylacetylenes *(10)* gives the vinyl cation *(11)* as intermediate stabilized by the α-aryl substituent (Markovnikov orientation)[13]. Aryl methyl ketones *(12)* are obtained quantitatively as the sole products. Kinetic studies, especially the large solvent isotope effects measured, demonstrate protonation of the triple bond in the rate-determining step.

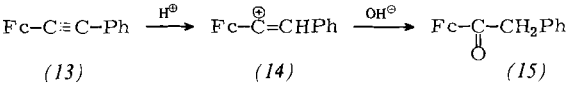


(10) *(11)* *(12)*

X = H, *m*- and *p*-halogen, *m*- and *p*-CH_3, CH_3O

Phenylacetylene reacts with HCl in glacial acetic acid at 25 °C to give α-chlorostyrene and acetophenone in the ratio of 12:1. Detailed mechanistic studies showed that under these conditions the addition proceeds exclusively by an Ad_E2 mechanism, *i.e. via* a vinyl cation[14]. Under different reaction conditions, the effect of solvent and added catalysts can cause the Ad_E3 mechanism to predominate. Thus, for instance, addition of HCl to deuterated phenylacetylene in CH_2Cl_2 with $ZnCl_2$ as catalyst gives mainly *syn* addition products[11,15].

The stabilizing effect of α-substituents on the intermediate vinyl cation is apparent from the acid-catalyzed hydration

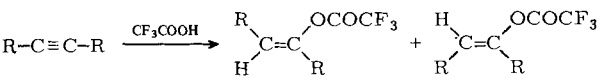


(13) *(14)* *(15)*

of ferrocenyl-phenylacetylene *(13)*[16]. Benzyl ferrocenyl ketone *(15)* is formed quantitatively, thus demonstrating the greater stability of the α-ferrocenylvinyl cation *(14)* as against the analogous α-phenylvinyl cation. Accordingly, the acid-catalyzed hydration of *(16)* is 10^5 times faster than that of *(17)*; protonation of the triple bond is the rate-determining step of this reaction.

(16) Fc—C≡CH Ph—C≡CH *(17)*

Detailed studies on the kinetics and products of addition of carboxylic acids, especially trifluoroacetic acid, to alkylacetylenes convincingly demonstrate the intermediacy of vinyl cations in these reactions. Thus 3-hexyne *(18a)* reacts non-stereospecifically with trifluoroacetic acid to form the vinyl trifluoroacetates (*Z*)-*(19a)* and (*E*)-*(19a)*, in the approximate ratio of 1:1, together with other products[17]. This result, along with specific substituent effects, was considered to constitute proof for the formation of vinyl cations on addition of trifluoroacetic acid. Other dialkylacetylenes, *e.g.* 2-butyne

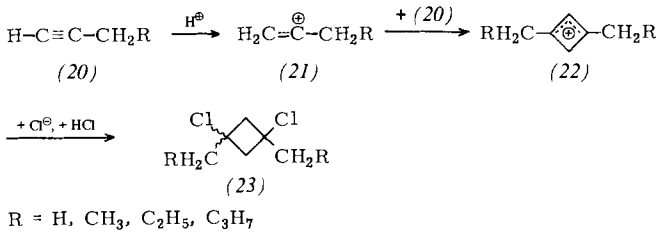


(18a), R = C_2H_5 (*Z*)-*(19)* (*E*)-*(19)*

(18b), R = CH_3

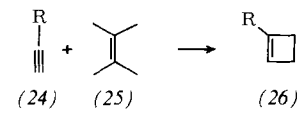
(18b), preferentially afford the (*Z*) isomer (*Z*)-*(19b)* on addition of trifluoroacetic acid. This is explained in terms of attraction between the β-methyl group in the intermediate vinyl cation and the attacking nucleophile[18].

Addition of anhydrous HCl and HBr to alkylacetylenes *(20)* in the liquid phase leads to interesting $[{}_{\pi}2_s + {}_{\pi}2_a]$ cycloaddition reactions, product formation being formulated *via* the vinyl cation *(21)*[19]. Reaction of *(21)* with the alkyne *(20)* gives the stereoisomeric cyclodimers *(23)* in good yields, presumably *via* the resonance-stabilized 1,3-disubstituted cyclobutenyl cation *(22)*. The normal mono- and di-adducts to the triple bond are also obtained. It recently also proved possible to prepare 1,3-dialkyl-1,3-dichlorocyclobutanes *(23)* contain-



R = H, CH_3, C_2H_5, C_3H_7

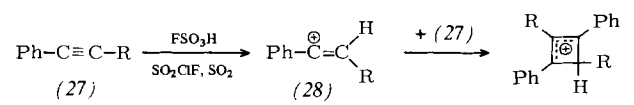
ing two different alkyl groups by reaction of mixtures of two alkynes[19c]. Alkylating cycloadditions proceeding *via* a vinyl cation intermediate also occur during the reaction of gaseous HCl with propene and propyne in the molar ratio 2:1:1[20]. In the presence of Lewis acids, 1-alkynes *(24)* react with alkenes *(25)* by cycloaddition to give cyclobutenes *(26)*. The catalytic effect of Lewis acids is probably due to complexation of the alkyne which leads to polarization in the sense of a vinyl cation[21].



(24) *(25)* *(26)*

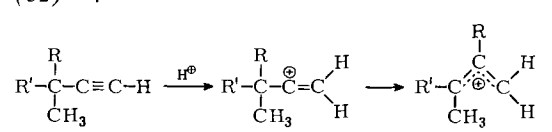
R = Alkyl

A detailed study of the addition of fluorosulfuric acid to alkynes in SO_2ClF at $-120\,°C$ or in SO_2 at $-78\,°C$ furnished the following picture[22]: terminal alkynes such as 1-butyne or 1-hexyne give solvent-separated ion pairs which react preferentially by *syn* addition to give vinyl fluorosulfates. In aryl-substituted alkynes *(27)*, stabilization *via* the adjacent aryl group leads to the vinyl cation *(28)*, which does not exist as an ion pair. The species *(28)* reacts with a second molecule of alkyne *(27)* to give cyclobutenyl cations *(29)*, which thus become readily accessible[23].



R = Ph, CH_3, *t*-Bu

Protonation of alkynes, *e.g. (30)*, with magic acid (FSO_3H—SbF_5) in SO_2ClF or SO_2 at $-78\,°C$ leads merely to oligomers; *i.e.* the intermediate vinyl cation *(31)* is insufficiently stable to be detected under these conditions. At higher temperatures, *e.g.* $-20\,°C$, it rearranges to the allyl cation *(32)*[24].



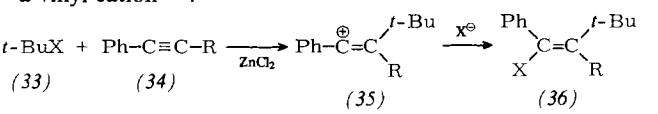
R = H, Alkyl; R' = Alkyl

2.1.2. Addition of Carbenium Ions

An Ad_E2 mechanism, *i.e.* vinyl cation formation, has also been demonstrated on addition of *tert*-butyl halides *(33)* to phenylacetylenes *(34)*[12, 15, 25].

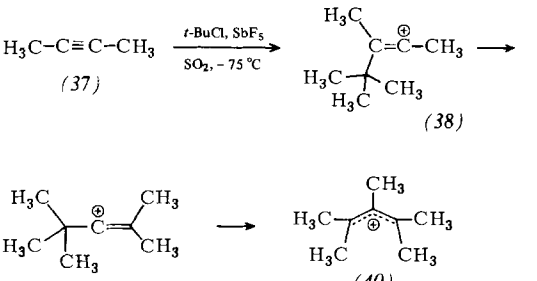
The *tert*-butyl cation formed by the action of the Lewis acid on *(33)* serves as electrophilic reagent. A linear vinyl cation *(35)* is formed as intermediate; it is preferentially attacked from the least hindered side by the nucleophile $X^{\ominus}$, giving products *(36)* with a high degree of stereoselectivity.

The same additions to mono- and di-substituted alkylacetylenes do not proceed in such a clear-cut fashion. The reaction products can also arise by pathways other than that involving a vinyl cation[26].

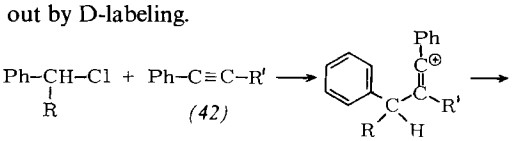


X = Cl, Br; R = Alkyl

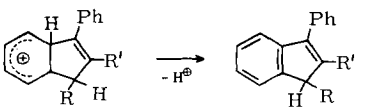
Addition of *tert*-butyl cation to 2-butyne *(37)* leads to an interesting rearrangement which was interpreted as a double 1,2-methyl shift[27]: the initially formed vinyl cation *(38)* undergoes a methyl shift across the double bond to give the



vinyl cation *(39)* which affords the allyl cation by a second methyl shift towards the double bond. Cation *(40)* was detected by NMR spectroscopy; a 1,3-methyl shift was ruled out by D-labeling.



(41a), R = Ph
(41b), R = H

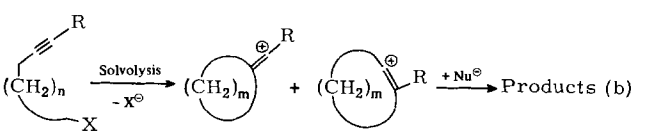


R' = Ph, CH_3

(44) *(45)*

Reaction of diphenylmethyl chloride *(41a)* and benzyl chloride *(41b)* with phenylacetylenes *(42)* in the presence of $AlCl_3$ (in CH_2Cl_2) illustrates the preparative utility of the addition of carbenium ions to triple bonds[28]. Substituted indenes *(45)* are obtained. The initially formed vinyl cation *(43)* cyclizes to *(44)*, yielding *(45)* on proton loss. Compound *(45)* is accompanied by the normal products of addition to the triple bond.

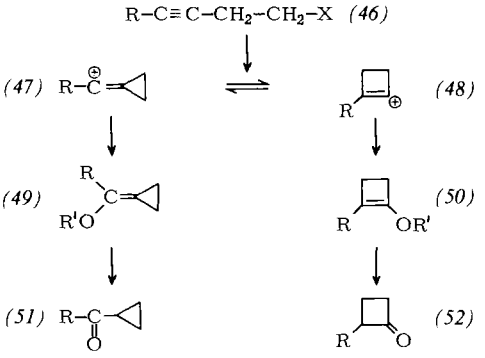
2.2. Participation of CC Triple Bonds in Solvolyses



R = H, Alkyl, Aryl; $X^{\ominus}$ = Halide, Sulfonate

Reactions of carbenium ions involving participation of CC double bonds have been known for several decades; the result-

ing cyclizations and kinetic effects have been established by a wealth of experimental material[29]. We first employed the CC triple bond as neighboring group in 1965 [see eq. (b)][30]: solvolysis of reactive homopropargyl derivatives *(46)* in solvents of high ionizing power and low nucleophilicity gives cyclopropyl ketones *(51)* and cyclobutanones *(52)*. In-depth mechanistic studies showed that the stabilized vinyl cations *(47)* and *(48)* are formed as intermediates, and react *via* the enol ethers *(49)* and *(50)* to give the ketones *(51)* and *(52)*[31].



(a), R = H; *(b)*, R = Alkyl; *(c)*, R = Aryl;
(d), R = Cyclopropyl
X = –O–SO₂–⟨⟩–CH₃(OTs), –O–SO₂–CF₃(OTf)

The product pattern obtained from this "homopropargyl rearrangement" depends upon the substituent R in *(46)*. Compounds *(46a)*, R=H, and *(46b)*, R=alkyl, give mainly the four-membered rings *(50a)* and *(52a)*, and *(50b)* and *(52b)*. In compounds *(46c)*, R=aryl, and *(46d)*, R=cyclopropyl, the stabilizing effect of these substituents on the intermediate cyclopropylidenemethyl cation *(47c)* and *(47d)* favors the three-membered ring derivatives *(49c)* and *(51c)*, and *(49d)* and *(51d)*, respectively[31].

The homopropargyl rearrangement is of preparative significance as a facile method for the synthesis of cyclobutanones, as will be illustrated by an example. The readily accessible compound 3-butynyl triflate *(46a)*, X=OTf, is heated to 50 °C in trifluoroacetic acid for 24 h; essentially pure cyclobutanone *(52a)* (yield 60 %) arises owing to the greater stability of *(48a)* compared with the primary vinyl cation *(47a)*[32]. 2-Alkylcyclobutanones *(52b)* are readily obtained in similar manner in high yield starting from *(46b)*[31a, 32]. The relatively high stability of cyclobutenyl cations *(48)* endows the homopropargyl rearrangement with considerable scope for the synthesis of cyclobutanones. Thus, starting from the corresponding homopropargyl derivatives, disubstituted cyclobutanones *(53)* and, *e.g.*, also condensed cyclobutanones *(54)* are accessible[31a, 33].



R = Alkyl

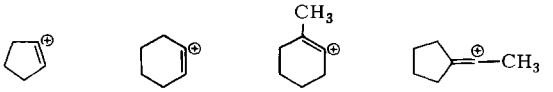
Cyclization reactions involving more distant triple bonds are also feasible. Table 1 lists the solvolysis products of some acyclic alkynyl triflates, showing how they depend upon the position of the triple bond relative to the functional carbon atom[34].

Table 1. Solvolysis of alkynyl triflates *(55)*—*(57)* in anhydrous trifluoroethanol.

R–C≡C–$(CH_2)_n$–CH_2–OSO_2CF_3 ⟶ cyclic products?
(55)—*(57)*

Cpd.	R	*n*	Cyclic products [%]
(55a)	H	2	0
(55b)	CH_3	2	0
(56a)	H	3	50 (Six-membered rings, *e.g.* 1-cyclohexenyl trifluoroethyl ether)
(56b)	CH_3	3	15 (Six-membered rings) 72 (Five-membered rings)
(57)	H	4	22 (Seven-membered rings)

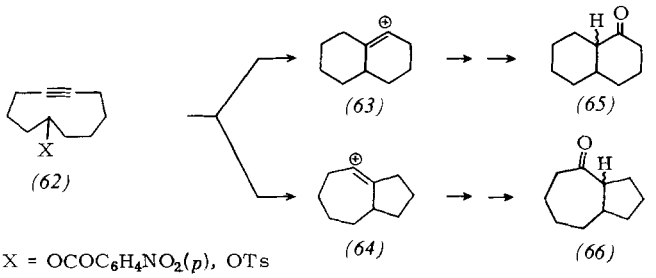
The triflates *(55a)* and *(55b)* solvolyze without cyclizing. Participation of the triple bond would lead to a cyclopentenyl cation *(58)*, whose formation in solvolysis reactions is unlikely. However, the triflate *(56a)* affords six-membered ring derivatives *via* the cyclohexenyl cation *(59)*; *(56b)* solvolyzes to give a mixture of six- and five-membered ring compounds formed from the vinyl cations *(60)* and *(61)*. The greater



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

stability of the linear vinyl cation *(61)* compared to the cyclic vinyl cation *(60)* leads to preferential formation of products derived from *(61)*. Compound *(57)* still solvolyzes with participation of the triple bond; however, only 22 % of seven-membered ring derivatives are formed owing to the length of the chain[35].

Transannular participation of a triple bond in medium-sized rings was first observed by us on solvolysis of 5-cyclodecynyl derivatives *(62)*[36]. These esters *(62)* also rearrange on solvol-

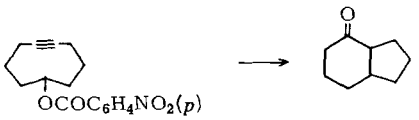


X = $OCOC_6H_4NO_2(p)$, OTs

ysis in comparatively nucleophilic solvents, *e.g.* in ethanol/water mixtures, to give mainly *cis*- and *trans*-1-decalone *(65)* while bicyclo[5.3.0]decan-2-one *(66)* is formed only in small quantities. The predominant formation of *(65)* is explained by the greater stability of the vinyl cation *(63)* compared with *(64)*[37].

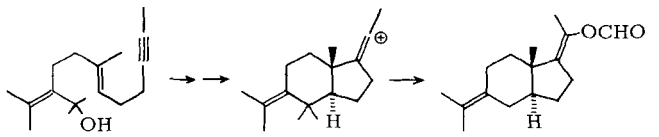
The proclivity of the triple bond to participate increases drastically in the 5-cyclononynyl derivative *(67)*; it solvolyzes 100 times as fast as *(62)* in 75 % aqueous ethanol, rearranging quantitatively to *cis*-4-hydrindanone *(68)* in spite of the pronounced nucleophilic nature of the solvent[38].

Syntheses of steroids and triterpenes by biomimetic cyclizations[39] have recently also been performed with systems involving triple-bond participation and vinyl cation interme-



(67) (68)

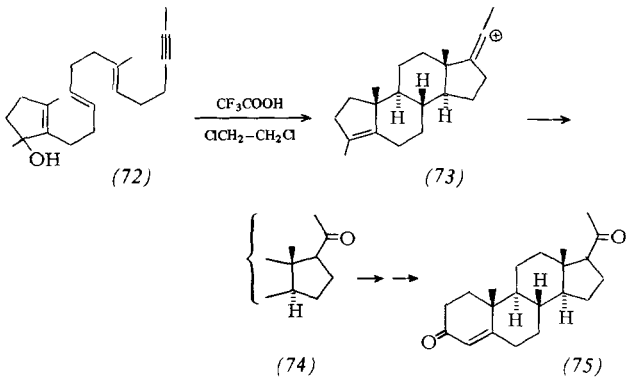
diates. Thus, treatment of the dienynol *(69)* with formic acid in pentane gives the enol formate *(71)* in 90% yield[40].



(69) (70) (71)

The acid attacks the tertiary OH group of *(69)*; the resulting carbenium ion cyclizes with participation of the double bond giving a new carbenium ion *via* formation of a six-membered ring. This ion is then transformed, with triple-bond participation, into the linear vinyl cation *(70)*.

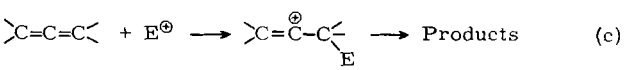
In the preparation of DL-progesterone *(75)*, the trienynol *(72)* is converted into the vinyl cation *(73)* in the final cyclization step involving the triple bond; *(73)* affords the ketone *(74)*[40]. Progesterone *(75)* can be obtained from *(74)* in two further steps.



(72) (73) (74) (75)

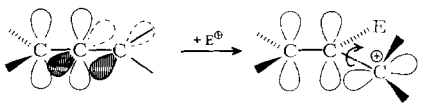
Other comparable cyclization reactions in which vinyl cations are formed have provided an entry to testosterone benzoate[41], and also to longifolene[42]. The high stereospecificity of the cyclization reaction has also been exploited for asymmetric syntheses[39].

2.3. Electrophilic Additions to Allenes



(c)

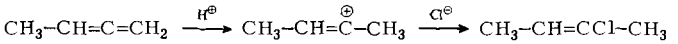
The cumulated double bonds of allenes permit electrophilic additions to follow various pathways. Additions to allene itself and to substituted allenes may proceed differently: addition to allene can give a vinyl cation, according to eq. (c), which has added the electrophile at the terminal carbon atom. In contrast, attack at the central carbon atom of the allene *(76)* would lead to a carbenium ion *(77)* which is formally an allyl cation and therefore appears preferentially. The carbenium ion *(77)*, however, is not a resonance-stabilized allyl cation. After attack of the electrophile $E^{\oplus}$ on the central carbon atom, a vacant p orbital is oriented perpendicularly on the remaining double bond as shown in *(77)*. Resonance



(76) (77)

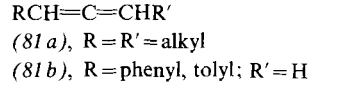
stabilization can only occur after a 90° rotation about the single bond in *(77)*. Additions to unsubstituted allene therefore proceed exclusively according to eq. (c)[43]. Thus acid-catalyzed hydration of allene gives only acetone, and addition of HCl and HBr to allene leads to the same products, including the cyclobutane derivatives, as are obtained on reaction of propyne with HCl under the same conditions. This suggests formation of the vinyl cation [eq. (c)][44-46].

Electrophilic addition is not so clear-cut with substituted allenes; intermediate formation of vinyl cations depends upon the number and nature of substituents and upon the electrophile. This situation is illustrated by a few examples of reactions between allenes and HCl: 1,2-butadiene *(78)* reacts at −78 °C with HCl with intermediate formation of the vinyl cation *(79)*[46], giving exclusively (*Z*)- and (*E*)-2-chloro-2-



(78) (79) (80)

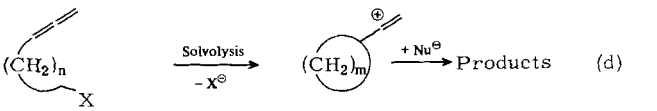
butene *(80)*. In contrast, only partial protonation of the terminal carbon atom occurs on reaction of 1,3-dialkyl-allenes *(81a)*. The ratio of terminal to central carbon protonation depends upon the reaction conditions[47]. Tetramethylallene no longer forms vinyl cation intermediates but, as expected, reacts *via* protonation of the central carbon atom to give a tertiary carbenium ion[48].



(81a), R = R′ = alkyl
(81b), R = phenyl, tolyl; R′ = H

Addition of HCl to arylallenes *(81b)* in glacial acetic acid also proceeds *via* protonation of the central carbon atom to form the more stable benzyl cation[49].

2.4. Participation of Allenic Groups in Solvolyses

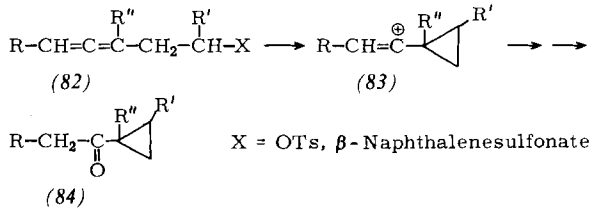


(d)

Equation (d) shows the participation of allenic groups in the generation of a carbenium ion. This reaction was first observed by us[50], and independently also by *Bertrand* and *Santelli*[51], in the solvolysis of homoallenyl derivatives *(82)*. Thus *(82)*, R = H, CH_3; R′ = R″ = H, gives mainly alkyl cyclopropyl ketones *(84)* in various solvents. Preferred cyclization to the ketones was rationalized in terms of intermediate formation of the stabilized cyclopropylvinyl cation *(83)*, owing to participation of the allenic bond in the solvolysis of *(82)*.

This reaction is known as homoallenyl rearrangement because of its resemblance to the homoallyl rearrangement.

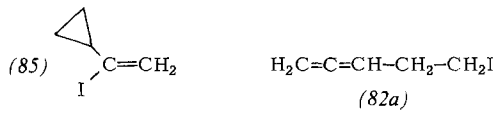
Subsequent systematic studies on the homoallenyl rearrangement showed that product formation depends upon the structure of the homoallenyl compound. While an alkyl attached to the functional carbon atom in *(82)*, R′ = alkyl,



(82) *(83)* *(84)*

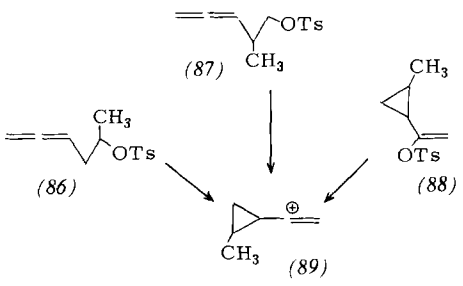
R″ = H, still leads to solvolysis products, among which the cyclopropyl alkyl ketone *(84)* predominates, doubly substituted homoallenyl derivatives *(82)*, R′ = R″ = alkyl, solvolyze preferentially to give cyclobutane derivatives[52]. Homoallenyl rearrangement to cyclopropyl ketones *(84)* has also been utilized preparatively[53].

The kinetics and products of solvolysis of cyclopropylvinyl derivatives (halides and tosylates) and isomeric homoallenyl derivatives led to the conclusion that stabilized cyclopropylvinyl cations are the initial intermediates in the solvolysis of homoallenyl derivatives. Thus cyclopropylvinyl iodide *(85)* and the isomeric homoallenyl iodide *(82a)* react under the



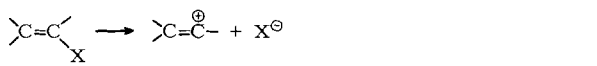
(85) *(82a)*

same conditions to give the same solvolysis products, which contain more than 65% of cyclopropyl derivatives[54]. Solvolysis of the tosylates *(86)*, *(87)*, and *(88)* in acetic acid gives products of very similar composition and stereochemistry whose formation is best explained by way of the cyclopropylvinyl cation *(89)*[55].



Participation of more distant allenic groups in solvolysis reactions also leads to cyclic products, which are not obtained, however, *via* vinyl cations as intermediates[56].

3. Formation of Vinyl Cations by Heterolysis

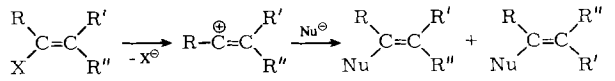


(e)

The reluctance of vinyl halides to undergo S_N1 reactions has a twofold explanation: it is attributed partly to the comparative instability of vinyl cations and partly to the ground state stabilization of vinyl halides. Stabilization of the ground state is a consequence of the higher s character of the carbon-halogen bond in vinyl halides (sp^2) compared with alkyl halides (sp^3)[57,58].

Solvolytic generation of vinyl cations [see eq. (e)] is feasible only if one of the following conditions is fulfilled: 1) Especially good leaving groups must be used for solvolysis, *e.g.* the "super-leaving groups" trifluoromethanesulfonate (triflate)[59] or the even more reactive nonafluorobutanesulfonate (nonaflate)[59]. 2) On use of leaving groups less prone to undergo S_N1 reactions, *e.g.* halides, then vinyl cations will only be formed if they are stabilized by a neighboring group with electron-donating ability.

In any case, it is necessary to establish that solvolysis of the vinyl compounds *(90)* investigated do actually proceed *via* vinyl cations. The pertinent mechanistic criteria can be briefly summarized as follows[60]: if a vinyl cation is formed in the rate-determining step of the solvolysis of *(90)* then the solvolysis must obey first-order kinetics. The rate of solvolysis is independent of solvent pH and of the concentration of added base, but dependent upon the ionizing strength of the solvent. The Winstein-Grunwald *m* value[61] should lie between 0.5 and 1.0. If the solvolysis is performed in deuterated solvents, then only a very slight solvent isotope effect, if any,



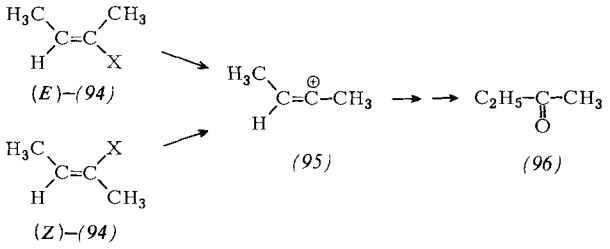
(90) *(91)* *(92)* *(93)*

is to be expected. Moreover, effects characteristic of carbenium ion mechanisms, such as salt effects, ion-pair formation, and phenomena of internal return have been observed. The linear geometry of the intermediate vinyl cation *(91)* suggests that the reaction products *(92)* and *(93)* are formed in equal quantities. Finally, the formation of rearranged products is a good mechanistic criterion for the course of the solvolysis reaction *via* vinyl cations.

Alternatively, the solvolysis products can be formed by, say, addition-elimination mechanisms; the initial step may comprise electrophilic addition of solvent, or possibly a nucleophilic addition of solvent to the double bond[60]. On solvolysis of a vinyl sulfonate, the product can also arise by nucleophilic attack of the solvent on the sulfonyloxy sulfur atom. If R′ or R″ = H in the vinyl derivative *(90)*, concerted β elimination often yields the alkyne.

3.1. Solvolysis of Simple Vinyl Derivatives with Particularly Good Leaving Groups

On replacement of halide as leaving group by the tosyloxy group, which has been thoroughly studied in the chemistry of saturated carbenium ions, intermediate formation of a vinyl cation can be accomplished by solvolysis of simple alkyl-substituted vinyl derivatives. Thus, for example, (*E*)-1-methyl-1-propenyl tosylate (*E*)-*(94)*, X = OTs, is solvolyzed in 50% aqueous methanol *via* the vinyl cation *(95)* to give a mixture of 2-butyne and 2-butanone *(96)*; in other solvents, such as acetic acid or formic acid, another mechanism is operative[62].

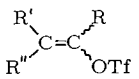


(E)-(94) (95) (96)

(Z)-(94)

The search for an even better leaving group led to the triflates[63] and nonaflates[59] which react some 10^4 times faster than tosylates. Acyclic secondary alkyl-substituted vinyl triflates and nonaflates solvolyze with few exceptions *via* intermediate vinyl cation formation: thus the vinyl triflates *(E)-(94)* and *(Z)-(94)*, X = OTf, react in ethanol/water mixtures, even at relatively low temperatures (76 °C), considerably faster than the tosylates *via (95)* to give the products [*e.g.* ketone *(96)*[64]].

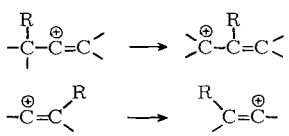
Systematic studies on the solvolysis reactions of the triflates *(97)* in solvents of various ionizing strengths and nucleophilicity revealed a pronounced carbenium ion character and no indication of a S_N2 reaction. The triflates *(97)* can solvolyze *via* ion-pair formation. This can lead to preferential formation of one stereoisomer in spite of expected formation of a linear vinyl cation intermediate[65].



(E)–, *(Z)*-*(97)*

R = CH_3, *i*-Pr, *t*-Bu; R′ = H, CH_3; R″ = H, CH_3

As in the solvolysis to give saturated carbenium ions, the solvolysis of vinyl derivatives is accompanied by rearrangements which can serve as evidence for an intermediate vinyl cation (see Section 3). Both rearrangements towards the double bond [eq. (f)] and rearrangements across the double bond are possible [eq. (g)].



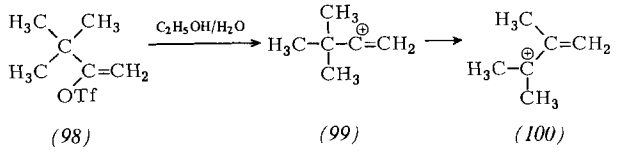
(f)

(g)

The driving force of the rearrangements is the formation of more stable carbenium ions. The rearrangements can involve shifts of alkyl and aryl groups; hydride shifts have also been observed. A few typical examples have been selected from the wealth of known rearrangements:

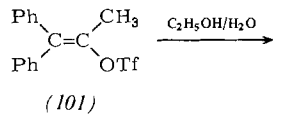
The vinyl triflate *(98)* solvolyzes in aqueous ethanol to give the vinyl cation *(99)*, which affords the saturated carbenium ion *(100)* by migration of a methyl group towards the double bond. The solvolysis products result mainly from *(100)* and only to a slight extent from the vinyl cation *(99)*[66].

Rearrangement across the double bond was observed on solvolysis of the vinyl triflate *(101)*. The initially formed vinyl cation *(102)* undergoes a phenyl shift, giving the vinyl cation *(103)* almost quantitatively. The positive charge in *(103)* is stabilized by the neighboring phenyl group; the ketone *(104)* is obtained on reaction with the solvent[67]. The β-aryl

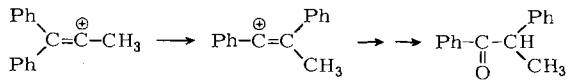


(98) *(99)* *(100)*

group participates in the rearrangement; under certain structural conditions, vinylenebenzonium ions *(105)* may be formed which correspond to the benzonium ions of saturated carbenium ion chemistry[68].

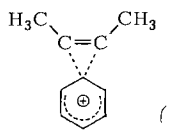


(101)



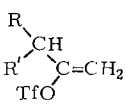
(102) *(103)* *(104)*

Hydride shifts towards the double bond have been found in the solvolysis reactions of the vinyl triflate *(106)*, and across the double bond in those of the vinyl triflates *(107)*.



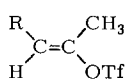
(105)

These processes afford a more stable carbenium ion and a more stable vinyl cation, respectively[69].



(106)

R = R′ = CH_3;

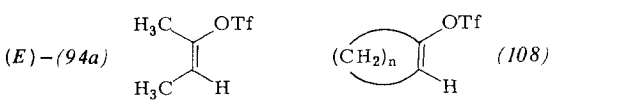


(E)–, *(Z)*-*(107)*

R = Ph, Cyclopropyl

Cyclic vinyl triflates also solvolyze with formation of vinyl cations. Table 2 shows examples of solvolysis rates as a function of ring size[70]. The cyclic vinyl triflates *(108)* solvolyze faster with increasing ring size, reaching a maximum rate with the nine-membered ring. The comparatively low reaction rate of 1-cyclohexenyl triflate is attributed to the impossibility of achieving the linear geometry required in the transition

Table 2. Rates of solvolysis of 1-cycloalkenyl triflates *(108)* in 50 % aqueous ethanol at 75 °C and of *(E)*-1-methyl-1-propenyl triflate *(E)-(94a)* [70].



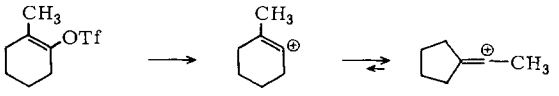
(E)-*(94a)* *(108)*

Cpd.	*n*	k [s^{-1}]	k_{rel}
(E)-(94a)		1.7×10^{-4}	1
(108)	4	1.2×10^{-8}	7.1×10^{-5}
(108)	5	4.2×10^{-5}	2.5×10^{-1}
(108)	6	4.5×10^{-4}	2.6
(108)	7	2.3×10^{-2}	135
(108)	8	3.3×10^{-3}	19
(108)	9	1.1×10^{-2}	65
(108)	10	6.8×10^{-3}	40

state for a vinyl cation with a ring of this size. In contrast, the 1-cyclooctenyl cation and cyclic vinyl cations having even more ring members can adopt a linear geometry as in the vinyl cation arising from (*E*)-*(94a)*. That the reaction rates of the cyclic vinyl triflates with more than eight ring members are higher than that of (*E*)-*(94a)* is probably due to a reduction of the *I*-strain in the transition state on formation of the vinyl cation. Qualitative comparison with the rates of solvolysis of 1-methylcycloalkyl chlorides appears in order[71]: a maximum rate of solvolysis was also found in the range of medium ring size which could be correlated with the strain energy of the medium-sized rings.

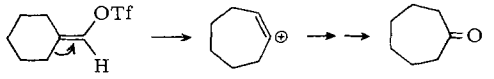
Rearrangements typical of a vinyl cation mechanism are again found in the solvolysis of cyclic vinyl triflates: 2-methyl-1-cyclohexenyl triflate *(109)* gives mainly the ring-contracted cyclopentyl methyl ketone on solvolysis in aqueous trifluoroethanol, the initially formed cyclic vinyl cation rearranging to the more stable linear vinyl cation *(110)*[72].

Cyclic vinyl cations are more stable than primary linear vinyl cations, as demonstrated by the solvolysis of the vinyl triflate *(111)* in aqueous trifluoroethanol: cycloheptanone



(109) *(110)*

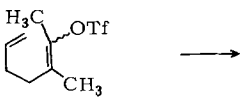
(113) is formed almost quantitatively *via* the cycloheptenyl cation *(112)*. Rearrangement to the cyclic vinyl cation *(112)* proceeds *via* a concerted ionization-alkyl shift without formation of a primary vinyl cation[73].



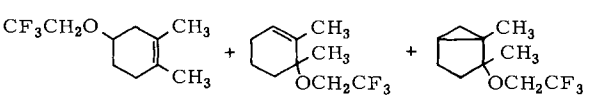
(111) *(112)* *(113)*

In contrast to cyclohexenyl triflate *(108)*, $n=4$, cyclopentenyl triflate fails to react by a vinyl cation mechanism in solvents of high ionizing strength, *e.g.* trifluoroethanol[74]. A cyclopentenyl cation *(58)* would be highly strained; it appears that the deviations from linear geometry no longer permit solvolytic generation of this intermediate.

The reactions of simple vinyl triflates described thus far are qualitatively reminiscent of the behavior of saturated carbenium ions. Two other reactions typical of saturated carbenium ion were also observed on solvolysis of vinyl triflates: thus solvolysis of the (*Z*)- and (*E*)-dienyl triflates *(114)* in trifluoroethanol gives not only acyclic products but also 20 to 35 % of the cyclic trifluoroethyl ethers *(115)*, *(116)*, and *(117)*, respectively, by participation of the double bond and formation of homoallyl-, allyl-, and cyclopropylmethyl cations[75].

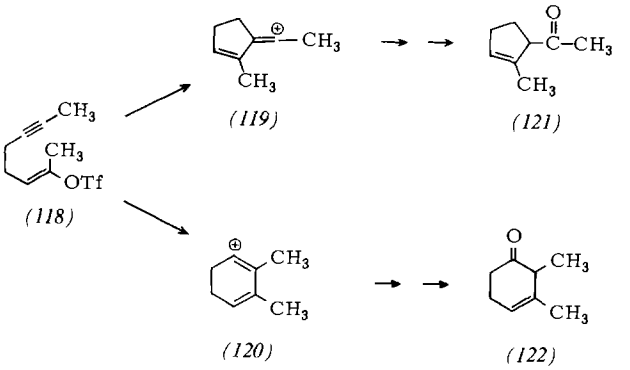


(*E*)–, (*Z*)–*(114)*



(115) *(116)* *(117)*

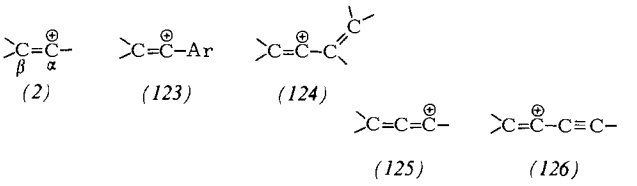
The enynyl triflate *(118)* solvolyzes in solvents of various ionizing strength with participation of the triple bond *via* the linear vinyl cation *(119)* giving mainly the ketone *(121)*. The cyclic vinyl cation *(120)* is only formed in minor amounts, as indicated by the low yields of ketone *(122)*[76].



(118) *(119)* *(120)* *(121)* *(122)*

3.2. Stabilized Vinyl Cations

Vinyl cations *(2)* are disubstituted carbenium ions. Stabilizing *C*-located substituents can be linked to C_α and C_β. Substituents on C_α give secondary vinyl cations. If C_β is formally part of the substituent group then especially stabilized cations are obtained, *e.g.* the allenyl cation *(125)* or the cyclopropylidenemethyl cation *(128)*.



(2) *(123)* *(124)* *(125)* *(126)*

Any substituents of proven efficacy in the case of saturated carbenium ions can be used to stabilize vinyl cations. Use of the aryl group as substituent gives the vinyl cation *(123)*.



(127) *(128)*

The stabilized cation *(124)* is obtained with a vinyl group. The effect of a neighboring triple bond in *(126)* has not yet been examined.

Vinyl cations are stabilized particularly well by nonclassical interaction with a cyclopropyl group as in *(127)* and *(128)*. The favorable geometry for overlapping of the orbitals involved confers a particularly high stability upon cyclopropylidenemethyl cations *(128)*.

With the exception of *(126)*, the vinyl cations *(123)* to *(128)* have been detected as intermediates in solvolysis reactions of the corresponding vinyl halides. Owing to the stabilizing neighboring groups, halide suffices as leaving group for the solvolytic generation of these vinyl cations (for a survey, see ref. [6]).

Other reactions involving intermediate formation of a vinyl cation by heterolytic bond rupture cannot be dealt with here; they are only of minor importance compared with the solvolyses of vinyl perfluoroalkylsulfonates described. For example, an attempt has been made to produce vinyl cations *via* dia-

zonium ions. A detailed account will be found in the reviews cited[5].

4. Generation of Vinyl Cations by Special Reactions

In this connection, mention should be made of, *e.g.*, photochemical reactions of vinyl iodides in which vinyl cations have been postulated as intermediates[77]. The reader is referred to the literature regarding this and a series of other reactions proceeding *via* vinyl cations[78].

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Mouse Histocompatibility Antigens

By Roland Henning[*]

In this article experimental findings and new theories concerning the chemical structure and biological function of histocompatibility antigens in the immune surveillance of virus-infected and malignant cells are discussed. Amongst these antigens, the H-2 antigens of the mouse have been studied most extensively. They are membrane bound glycoproteins causing the rejection of transplants from foreign tissue. One future aim of this field of research is to utilize the immune surveillance system in the therapy of diseases which as yet cannot be treated.

1. Introduction

Histocompatibility antigens are membrane bound glycoproteins which are responsible for the rejection of tissue transplants from foreign organisms. Recent results suggest that these membrane proteins participate in immune reactions in order to protect the body against virus infections and tumor formation. These antigens are polymorphic proteins which, in the mouse, are coded for in the histocompatibility complex located on chromosome 17 (see Fig. 1). Many findings made on this system which has been investigated best in the mouse, can also be demonstrated in the largely analogous human HL-A system.

Experimentally sound and properly interpreted observations on tissue rejection date from the turn of the century[1] when inbred mice strains (*i.e.* genetically uniform animal material) were reared. Mice from such an inbred strain are almost like identical twins. In 1938 *Gorer*[2] investigated the blood group system of the mouse and found that the antigen II which he had described correlated with tissue rejection and was genetically determined. This antigen II was later renamed the H-2 antigen[3]. In 1944 *Medawar*[4] described the phases of tissue rejection and applied these observations to human skin transplantations. The introduction of congenic inbred strains by *George D. Snell*[5] was the next critical step. Congenic strains are, for example, two inbred strains of mice which differ at only one locus in the histocompatibility complex. Antibodies specifically directed against a single gene product of the histocompatibility complex (alloantibodies) can be produced by cross immunization of such congenic strains. These alloantisera are the main tools of modern transplantation serology and with their aid histocompatibility antigens can be characterized, isolated and chemically investigated with a high degree of specificity.

Using immunogenetic methods, it was established that histocompatibility antigens and the specificity of humoral immune responses are often closely coupled. From this it was concluded that the responsible genes involved (Ir genes) must be coded for on the same chromosome as the H antigens[6]. In 1971 *Klein* and *Shreffler* put forward the hypothesis[7] that the histocompatibility antigen responsible for tissue rejection is coded for by two loci, the K and the D loci, which are on chromosome 17 of the mouse (two locus model). In addition to the K and D loci, the histocompatibility complex contains the above mentioned I region and also the S region. The latter codes for a certain component of the complement system. Figure 1 gives a schematic summary of the organization of the histocompatibility complexes on chromosome 17 of the mouse and chromosome 6 of man.

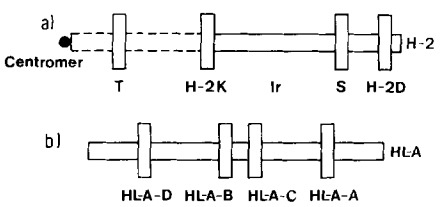


Fig. 1. H-2 and HL-A gene complexes (histocompatibility complexes). a) The H-2 gene complex on chromosome 17 of the mouse is limited by the K and D loci. The I and S regions are located within the gene complex. b) The HL-A gene complex on chromosome 6 of man is similar to the H-2 gene complex of the mouse apart from the fact that the HL-A-D region, which corresponds to the I region of the mouse, lies outside the loci HL-A-A and HL-A-B. The latter two loci are equivalent to the K and D loci of the mouse (according to [8]).

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2. Chemical Structure of the H-2 Antigens

The histocompatibility antigens of the mouse (H-2 antigens) are found on almost all cells and in highest concentration on lymphocytes[8]. These substances are characterized by an extremely high, genetically determined polymorphism which is expressed by a variability in the amino acid sequence. H-2 antigens are integral membrane glycoproteins which consist of at least two polypeptide chains—a heavy chain with a molecular weight of approximately 45000[9] and a light chain with a molecular weight of 12000. The heavy chain (a glycopolypeptide) carries the antigenic properties. The light chain (a polypeptide) corresponds to β_2-microglobulin isolated from human urine[10]. In the mouse and man both chains are non-covalently associated[11–13].

2.1. Molecular Structure of H-2 Antigens in Solution

The following properties of the H-2 antigens make their isolation difficult: 1. their genetically determined polymorphism, 2. their low concentrations on the cell surface membrane and 3. their insolubility in aqueous media. Normal mouse lymphocytes or mouse leukemia cells which can be permanently maintained in culture are used as starting material.

H-2 antigens can be extracted from these cells with detergents (*e.g.* Nonidet P 40, sodium deoxycholate[14]) with little or no loss in their antigenic properties. Water soluble, fully immunologically active fragments of H-2 antigens can also be obtained by controlled proteolytic digestion of the cell surface with the plant protease papain[15].

Due to their low concentrations, H-2 antigens are preferably isolated after they have been radioactively labeled. Cells which have been labeled with ^{125}I or with ^{3}H- or ^{14}C-labeled amino acids are best for this purpose. H-2 antigens can be isolated from detergent or papain extracts of these labeled cells by immunoprecipitation and can be examined by SDS polyacrylamide gel electrophoresis. The molecular weights of the polypeptide chains and the nature of the binding between them are determined in this electrophoresis system with or without reducing agents (Table 1)[16].

On polyacrylamide gels of detergent-solubilized H-2 antigen ($H\text{-}2_{det}$) in the presence of reducing agents, a heavy chain (H chain) of molecular weight 46000 and a light chain (L chain) of molecular weight 12000 are observed. In the absence of reducing agents, the molecular weight of the heavy chain in the SDS gel is doubled (approximately 92000). After re-electrophoresis of this material in the presence of reducing agents (*e.g.* mercaptoethanol), only a heavy chain with a molecular weight of 46000 is found. Therefore, the heavy chains of H-2 antigens in detergent solution must be linked by at least one disulfide bridge to form a dimer. The light chains are not covalently bonded either to the heavy chains or to each other. Antigens solubilized with papain ($H\text{-}2_{pap}$) contain only a fragment (F_H) of the heavy chain with a molecular weight of 39000 and an intact light chain. In papain-solubilized material no disulfide bridges are found between the fragments of the heavy chain.

The molecular weights of H-2 antigens can also be determined under non-denaturing conditions (Table 1) by gel chromatography and ultracentrifugation[16]. Under these conditions the antigens can be monitored in their biologically active form by means of a biological test—the cytotoxicity inhibition test. The molecular weight of H-2 antigens in detergent solution was calculated to be 116000. From the determination of the molecular weights of the individual polypeptide chains by SDS gel electrophoresis and of the biologically active molecule in detergent solution a working model (Table 1 and Fig. 2) for the molecular structure of the H-2 antigens can be postulated[16]. In detergent solution there are two heavy chains which are linked by at least one disulfide bridge and two non-covalently associated light chains. The papain-treated molecule contains only one fragment of a heavy chain (F_H) and one light chain. Similar findings hold for the human HL-A antigens.

Table 1. Molecular weight (M_r) determinations of denatured H-2 antigens by SDS gel electrophoresis and of biologically active H-2 antigens in detergent or papain solution by Sephadex gel chromatography ("gel filtration") and ultracentrifugation [16]. Abbreviations: r = Stokes radius; D = diffusion constant; S = sedimentation constant; DOC = Na deoxycholate; SDS = polyacrylamide gel electrophoresis in Na dodecylsulfate; red. = reduced with mercaptoethanol; H chain, L chain, β_2, F_H see Fig. 2.

Antigen	M_r	Gel filtration		Ultracentrifugation
		r [Å]	D [$cm^2\,s^{-1}$]	S
Detergent-solubilized H-2-antigens (DOC) ($H\text{-}2_{det}$)	116000 [a]	47	$4.5\cdot10^{-7}$	5.9 S
H-chain (unreduced, SDS)	92000			
H-chain (reduced, SDS)	46000			
L-chain (β_2) (red. + unred., SDS)	12000			
2H + 2L (SDS)	116000			
Papain-solubilized H-2-antigens ($H\text{-}2_{pap}$)	49000	31	$6.9\cdot10^{-7}$	3.7 S
H-chain (F_H) (red. + unred., SDS)	39000			
L-chain (β_2) (red. + unred., SDS)	12000			
1 F_H + 1 L	51000			

[a] Calculated according to the Svedberg equation.

2.2. Molecular Structure and Orientation of H-2 Antigens at the Cell Surface

The biological functions of H-2 antigens are expressed on the cell surface. It is therefore extremely important to know whether the structural model for the solubilized H-2 antigens

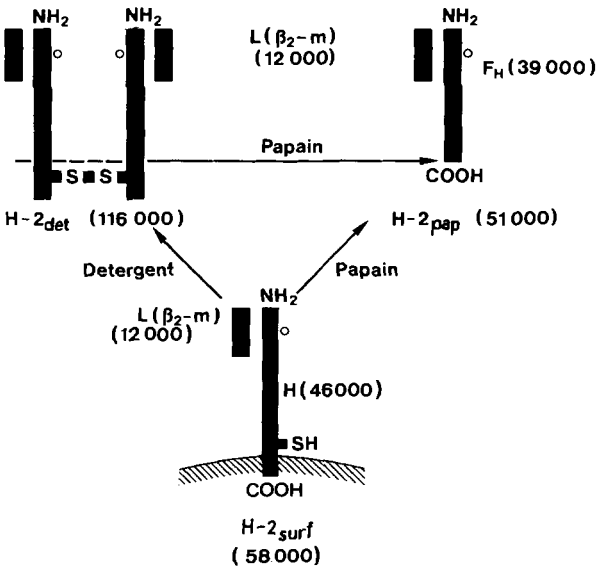


Fig. 2. A model of the molecular structure of H-2 antigens on the cell surface and in solution. The H-2 antigens are solubilized with non-ionic detergents or papain. Abbreviations: L(β_2 – m) = light chain (corresponds to β_2-microglobulin); H = heavy chain; $H\text{-}2_{pap}$ = water soluble fragment after papain treatment; F_H = papain fragment of the H chain; $H\text{-}2_{det}$ = detergent-solubilized H-2 antigen; $H\text{-}2_{surf}$ = H-2 antigen at the cell surface; ○ = carbohydrate. The molecular weights are given in brackets (modified according to [16]).

is equally applicable to the antigens bound to the cell surface. In order to establish whether H-2 antigens at the cell surface are also dimers with disulfide bridges, intact cells were treated with iodoacetamide before detergent extraction; free SH groups are thus already blocked on the surface of the intact cells[16]. If immunoprecipitates of these alkylated cells are examined by SDS gel electrophoresis, it is seen even in the absence of reducing agents that the heavy chains of the H-2 antigens exist mainly as monomers whereas, as has already been mentioned, the heavy chains of H-2 antigens from non-alkylated cells are disulfide linked dimers. This implies that the disulfide bridges are formed during or after detergent extraction of the antigen from the cell membrane (Fig. 2). Non-covalently associated dimers are perhaps already formed in the membrane. Mild oxidizing agents can initiate the formation of disulfide bridges between heavy chains and thus increase the concentration of membrane-bound, disulfide-bonded dimers[16]. Apparently however, dimer hybrids (*e.g.* between the products of the K and D loci or between the K and D antigens of different H-2 types (haplotypes)[17,18]) are not formed.

The orientation of the peptide chains of the H-2 antigens on the cell membrane is also very important for understanding their biological functions. For this purpose the N-terminal amino acid sequence of the heavy chains of the detergent-solubilized H-2 antigens is compared with that of the F_H fragment from the papain-cleaved material. Using this method it can be shown which end of the heavy chain is directed outwards and which end is associated with the cell membrane. Radiochemical sequence analyses of the heavy chains and their papain fragments demonstrate that the positions of tyrosine, histidine and arginine (positions 3, 6 and 7 respectively) are identical[16]. From this it can be concluded that the C-terminal end of the H-2 antigen is associated with the membrane and is cleaved off during papain treatment so that a new C-terminal end is formed on the cleaved fragment. Consequently, the N-terminal end is directed outwards. This arrangement resembles the orientation of the few sequenced membrane proteins (*e.g.* glycophorin or immunoglobulin[19–21]). Figure 2 shows the present concepts of the molecular anatomy of H-2 antigens.

2.3. Comparison of the Protein Chemistry of the H-2K and H-2D Gene Products

According to the results of immunogenetic analyses, it can be assumed that the H-2K and H-2D genes arose by gene duplication[7]. Can a molecule be recognized as being a K or D antigen solely on the basis of its physical or chemical properties? It is conceivable that the differences between the two types of gene products could be established by the following methods: 1. molecular weight determination of the heavy chains, 2. comparative peptide analyses after enzymatic cleavage, 3. amino acid sequence analyses.

Comparison of the behavior of the heavy chains of the K or D antigens on SDS polyacrylamide gel electrophoresis shows slight but exactly reproducible differences. On a molecular weight scale these small differences never amount to more than approximately 5 %[22]. These variations cannot be interpreted with certainty as being due to differences in molecular weight, they could also be explained by differing binding capacities for SDS due to different carbohydrate structures. The behavior of the heavy chains on fragmentation with clostridiopeptidase, papin or chemical methods exhibits characteristic features for each gene product; neither in this case, however, is it possible to derive generally valid rules which could serve as criteria for the recognition of K or D gene products[22].

Comparative peptide analyses of tryptic fragments of different H-2 antigens on ion exchange columns[14] or by two-dimensional thin layer chromatography[22] give the same results. These peptide analyses show a high degree of similarity which is to be expected in the case of gene duplication; the differences are not however characteristic of the K or D gene products. The results of amino acid sequencing will be fully discussed below. In summary it can be said that, as yet, there are no unequivocal physical or chemical criteria for distinguishing between the K and D gene products.

Fundamental questions concerning the molecular principles of polymorphism, the evolutionary relationships between histocompatibility antigens and immunoglobulins, and finally the molecular biology of their function can be answered solely by unravelling the primary structure of the antigenic units of the H-2 antigens.

The complete amino acid sequence of human β_2-microglobulin has been reported[23,24]. This molecule shows very striking similarities with the constant regions of the heavy and light chains of immunoglobulins. This finding has restarted speculation about a common evolutionary origin for histocompatibility antigens and immunoglobulins (cf. Section 1)[25,26]. β_2-Microglobulin is only species specific (*i.e.* no differences have been found between individuals of the same animal species). The variation between species is not very marked. If the amino acid sequences of the microglobulins from the guinea pig, rabbit, dog and mouse are compared with that of man, only a few differences are observed[27]. These amino acid sequences are compiled in Table 2.

The polymorphism, and thus the antigenic properties of the H-2 antigens, are limited to the heavy chains. Their low concentrations together with the hydrophobic nature of the K and D antigens, demanded a new approach for their isolation and sequence analysis. Conventional Edman degradation techniques cannot be directly applied to establish their primary structures; radiochemical sequencing methods must be used[28]. The technique of indirect immunoprecipitation with monospecific H-2 antisera was utilized to isolate the K and D antigens. H-2 antigens from mouse lymphoma cells are individually labeled in tissue culture with either ^{3}H- or ^{14}C-labeled amino acids. The cells are then extracted with the detergent Nonidet P 40. The antigenic properties of the H-2 antigens are not affected by non-ionic detergents, the H-2 antigens can be precipitated out of the mixture of labeled proteins by a monospecific mouse anti-H-2 antiserum and subsequent addition of goat anti-mouse immunoglobulin. Subsequently, the antigens are isolated by preparative SDS polyacrylamide gel electrophoresis. After addition of a carrier protein, this material can be subjected to sequential Edman degradation in an automatic protein sequencer. The resulting phenylthiohydantoin amino acids can be identified by thin layer chromatography or high pressure liquid chromatography (for a discussion of this methodology see[22]). The N-terminal amino acid sequences of the H-2 and HL-A antigens are compiled in Table 2.

Table 2. Comparison of the partial N-terminal amino acid sequences of H-2 antigens (mouse) [16, 22, 29—32, 74], HL-A antigens (human) [33—35] and β_2-microglobulins (human, rabbit, dog, mouse and guinea pig) [23, 24, 70—73]. X: Amino acids which have been identified at this position in other H-2 haplotypes were not found in this location. □: These positions are common to H-2 and/or HL-A antigens and/or β_2-microglobulins.

		1				5					10				15
H-2	K^b	X	Pro	His	—	Leu	Arg	Tyr	Phe	Val	Thr	Ala	Val	—	Arg	Pro
	K^d	Met	X	His	—	X	Arg	Tyr	X	X	Thr	—	X	—	Arg	Pro
	K^k	Met	Pro	His	—	Leu	Arg	Tyr	Phe	His	—	Ala	Val	—	Ile	Pro
	D^b	—	Pro	—	—	—	Arg	Tyr	—	—	—	Ala	Val	—	Arg	Pro
	D^d	Met	X	His	—	Leu	Arg	Tyr	Phe	Val	Thr	Ala	Val	Thr	Arg	Pro
HLA	A2	Gly	Ser	—	Ser	Met	Arg	Tyr	Phe	Phe	Thr	Ser	Val	Ser	Arg	Pro
	A1,2	—	Ser	—	Ser	Met	Arg	Tyr	Phe	Phe	Thr	Ser	Val	Ala	Arg	Pro
	B7	Gly	Ser	His	Ser	Met	Arg	Tyr	Phe	Tyr	Thr	Ser	Val	Ser	Arg	Pro
	B8,13	—	Ser	—	Ser	Met	Arg	Tyr	Tyr	Tyr	Ser	Ala	Val	Ser	Arg	Pro

β_2-Microglobulin															
Man	Ile	Gln	Arg	Thr	Pro	Lys	Ile	Gln	Val	Tyr	Ser	Arg	His	Pro	Ala
Rabbit	Val	Gln	Arg	Ala	Pro	Asn	Val	Gln	Val	Tyr	Ser	Arg	His	Pro	Ala
Dog	Val	Gln	His	Pro	Pro	Lys	Ile	Gln	Val	Tyr	Ser	Arg	His	Pro	Ala
Mouse	Ile	Gln	Lys	Thr	Pro	Gln	Ile	Gln	Val	Tyr	Ser	Arg	His	Pro	Pro
Guinea pig	Val	Leu	His	Ala	Pro	Glx	Val	Gln	Val	Tyr	—	—	His	Pro	Ala

				20					25				30			
—	Leu	—	—	Pro	Arg	Tyr	—	—	—	Leu	Tyr					
—	X	—	—	Pro	Arg	Phe	—	—	—	—	Tyr					
—	Leu	—	Lys	Pro	Phe	Ala	—	—	—	—	Tyr					
—	Leu	—	—	Pro	Arg	Tyr	—	—	—	—	Tyr					
—	—	—	—	Pro	Arg	Tyr	—	—	—	—	Tyr					
Gly	—	Gly	Glu	—	—	Phe	Ile	Ala	Val	—	—					
Gly	—	—	—	—	—	—	—	—	—	—	—					
Gly	Arg	Gly	Glu	Pro	Pro	Phe	Ile	Ala	Val	Gly	Tyr	Val	Asp	Glu	Thr	
Gly	—	—	—	—	—	—	—	—	—	—	—					
Glu	Asn	Gly	Lys	Ser	Asn	Phe	Leu	Asn	Cys	Tyr	Val	Ser	Gly	Phe	His	
Glu	Asn	Gly	Lys	Asp	Asn	Phe	Leu	Asn	Cys	Tyr	Val	Ser	Gly	Phe	His	
Glx	Asx	Gly	Lys	Pro	Asx	Phe	Leu	Asx	Cys	Tyr	Val	Ser	Gly	Phe	His	
Glu	Asn	Gly	Lys	Pro	Asn	Ile	Leu	Asn	Cys	Tyr	Val	Thr	Glu	Phe	His	
Glu	Asn	Gly	—	—												

All five H-2-gene products given in Table 2 have N-terminal amino acid sequences which are largely homologous within the first 30 positions. This observation supports the theory proposed by *Klein* and *Shreffler* in 1971[7] which states that the K and D loci arose by gene duplication. The homology of the N-terminal sequences is so extensive that the expected polymorphism can be recognized only at a small number of positions. In addition to the positive differences, it was also shown that certain amino acids were absent in individual gene products (positions indicated by X in Table 2). The absence of methionine from position 1 in K^b, of proline, valine and valine from positions 2, 9 and 12 respectively in K^d are examples of such negative variations. The amino acids in these positions have still not been identified due to the limitations of the methodology.

H-2 and HL-A antigens apparently are structurally homologous. The N-terminal amino acid sequences of several HL-A gene products were reported almost simultaneously by two laboratories[33–35]. Sequence analyses of the HL-A antigens were performed by conventional Edman degradation methods. If the N-terminal sequences of H-2 and HL-A antigens are aligned, it can be seen that the same amino acids can be found in at least 13 of the first 27 positions. The amino acids in positions 6, 7, 15, 20 and 27 are the same in all cases. In positions 8, 10, 12 and 14 the variation is small. The products of the two gene loci of one system (*e.g.* the H-2 system) resemble one another much more than the products of the corresponding loci from other species. From this, it can be concluded that gene duplication in the two species mouse and man took place independently and after the evolution of the species had occurred. From Table 2 it can also be seen that the H-2 and HL-A antigens have several positions in common with those of β_2-microglobulins from various species. Although it can be presumed that β_2-microglobulins are evolutionarily related to the heavy chains of the histocompatibility antigens, the sequence homologies shown in Table 2 only allow very vague conjectures to be made about the extent of this relationship.

The long suspected structural homologies between immunoglobulins and histocompatibility antigens have recently been shown to be probably correct. Partial amino acid sequences of internal peptides from the heavy chains of HL-A antigens have been examined[35]. *Strominger et al.* found extensive sequence homologies with the immunoglobulins in the vicinity of the third cysteine residue of the heavy chain of HL-A antigens (see Fig. 3) and thus, could provide evidence for the long discussed theories of evolutionary and structural relationships between the two systems[25, 26]. The tentative positions of the intrachain disulfide bridges also suggest that there is a structural and therefore an evolutionary

relationship between histocompatibility antigens and immunoglobulins (Fig. 3).

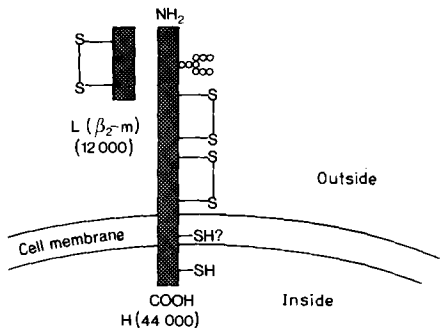


Fig. 3. Model of an HL-A antigen on the cell surface (modified according to [35]). This model indicates the position of the disulfide bridges in the heavy chains which, like the immunoglobulins, are arranged in a "domain structure". The binding site for β_2-microglobulin in the N-terminal region is a theoretical assumption and is not based on experimental findings.

The supposition that there is an evolutionary relationship between H antigens and immunoglobulins is also supported by the additional sequence homologies which have recently been established between immunoglobulins, C-reactive protein and components of the complement system[36, 37] all of which belong to the immune system. Phylogenetic studies of the individual components suggest that the histocompatibility antigens appeared earliest in evolution. Biological evidence for transplantation immunity has recently been obtained from coral reefs[38]. Transplanted sections of coral reefs are rejected and, what is more important, on repeated transplantation this occurs in a considerably shorter time (immunity including memory).

The application of the radiosequencing technique to H-2 antigens obtained by highly specific immunoprecipitation methods soon yielded a series of fundamental results. A completely new methodology was developed for the investigation of the primary structure of membrane proteins which had, until then, remained inaccessible to structural analysis. Thanks to the method of isolation by immunoprecipitation, all cell membrane antigens against which specific antibodies can be raised are now open to detailed structural studies. In the human HL-A system structural homologies between immunoglobulins and histocompatibility antigens could be demonstrated by conventional sequencing procedures as a result of higher concentrations of HL-A antigens on lymphoma cells.

3. Histocompatibility Antigens as Recognition Sites in Immune Defense

The transfer of tissues between individuals fails due to histocompatibility antigens which constitute the biological barrier for tissue transplants. Special cells of the immune system, T lymphocytes which are transformed into killer cells, destroy foreign cells; this is one basic principle of the cellular immune response. Tissue transplantation did not contribute to the evolutionary process and, therefore, one can assume that these very potent defense mechanisms must perform an important function within the individual organism[25]. Transplantation antigens seem to be marker proteins for distinguishing abnormal cells from the individual's own, normal cells. According to the most recent findings, H-2 antigens are involved in the recognition and destruction of abnormal cells by cytotoxic lymphocytes. Examples of abnormal cells which must be recognized and eliminated are virus-infected cells, chemically modified cells and tumor cells.

3.1. Histocompatibility Antigens are Necessary for the Elimination of "Foreign" Cells

The effectiveness of cytotoxic cells produced to act against abnormal cells seems to depend on whether an H-2 antigen originally present on the cells used for immunization also exists on the target cell[39]. The following model experiment should serve to explain this complicated process: an inbred mouse (which has for example type H-2^b histocompatibility antigens) is infected with virus X and cytotoxic lymphocytes directed against the virus-X-infected cells are produced in the animal. The lytic activity of these lymphocytes can be detected by a cytotoxicity test in which the release of ^{51}Cr from ^{51}Cr-labeled target cells is followed. In the present experiment only those ^{51}Cr-labeled target cells are recognized and killed which (*i*) are infected with the same virus X and (*ii*) have the same type H-2^b histocompatibility antigens as the virus-X-infected cells[39]. The model experiment described has been tested on a large number of different type H-2 mouse strains and cell lines with several viruses (ectromelia[40], lymphocytic choriomeningitis[41], Sendai[42], SV-40[43], rabies[39], mouse sarcoma[44], Friend's mouse leukemia[45] and vaccinia[46]). In most cases a clear dependence on the type of H-2 antigen was observed (H-2 restriction). Similar results were found by chemical modification of the cell surface with trinitrobenzenesulfonic acid (TNB)[47]. The universal importance of these observations was further underlined by similar findings made on virus transformed tumor cells[48–50].

These observations can be summarized as follows:

1. If the cytotoxic cell and the target cell are syngeneic (*i.e.* their surfaces carry the same H-2 antigens), an additional antigen (neoantigen) is required for the recognition and destruction of the target cell (*e.g.* a virus antigen, a chemically modified protein or a tumor antigen, one of the weak H antigens[51, 52] or the product of the Y gene[53]).

2. If the histocompatibility antigens of the cytotoxic lymphocyte and the target cell are different (allogeneic situation), an additional antigen is not necessary for recognition and destruction of the target cell. This situation corresponds to that in tissue transplantation.

3. Cytotoxic lymphocytes must have been confronted with at least one H-2 gene product (K or D) of the target cell during the immunization process.

4. Anti-H-2 sera which are directed against the H-2 antigens of the target cell and are added to the target cells before contact with the cytotoxic lymphocytes, block the activity of the cytotoxic lymphocytes; the target cell is not destroyed.

5. Mutations in an H-2 antigen known to the cytotoxic lymphocytes, block all cytotoxic activity; the target cell is not destroyed[57].

A greatly simplified hypothesis explaining these findings would be that all the processes in cell destruction which are directly dependent on cytotoxic lymphocytes proceed only with the aid of the H-2 antigens. The reaction mechanisms in both the syngeneic and allogeneic situations seem to be the same. In the allogeneic case only the foreign H-2 antigen

and not the additional neoantigen is necessary for recognition. From this it could be concluded that an H-2 antigen which has been modified by the neoantigen ("altered self")[39] is employed for recognition of the foreign material in the syngeneic case.

3.2. "Killer" Cells Require One or Two Receptors for the Destruction of Target Cells

In 1959 *Lawrence* had already put forward an hypothesis according to which abnormal cells in an individual can only be destroyed in a cytotoxic reaction if, in addition to a known antigen, an antigen X is recognized[54]. This "self" plus X antigen was supposed to form a molecular complex and corresponds in principle to what, much later, was described as the basis of T-B cell collaboration[55, 56]. According to present experimental findings, virus-coded antigens and tumor transplantation antigens (see Figs. 6 and 7) can act as X antigens and together with H antigens as "antigen hybrids", serve as recognition sites.

Two hypotheses explaining these processes are currently under discussion. How can cytotoxic lymphocytes recognize only one antigen (the alloantigen) in an allogeneic situation and the syngeneic antigen + neoantigen in a syngeneic situation? In the syngeneic situation it has to be assumed that the cytotoxic lymphocyte possesses two separate receptors (two-receptor model)—one receptor for the recognition of the syngeneic H-2 antigen and another for the neoantigen. It could also be possible, however, that the cytotoxic lymphocyte has only one receptor which recognizes a molecular complex formed from the H-2 antigen and the neoantigen (antigen hybrid) or a modified H-2 antigen ("altered self") (one-receptor models). In the allogeneic situation only one receptor is required, and therefore a theory must be postulated in which one receptor in the syngeneic situation is sufficient.

3.3. "Killer" Cells with One Receptor for the Destruction of Target Cells

Some experiments which support the one-receptor model will now be briefly described. Due to spatial considerations (*i.e.* the maximum possible length of a protein receptor), it is necessary that a molecular complex consisting of the H-2 antigen and the neoantigen is formed. The antigenic determinant is either a cell product, namely the H-2 antigen, which has been modified by physical or chemical interaction with the neoantigen or is one determinant formed from both the H-2 antigen and the neoantigen (H-2-antigen-virus-antigen hybrid complex). Since, in this case, the H-2 antigens still react with the relevant monospecific H-2 antisera and the cytotoxic reaction can thus be blocked, it must be presumed that the serological properties of the H-2 antigens have not been altered. The modification therefore cannot be due to drastic chemical changes but to slight alterations which do not affect the antigenic determinants. Chemical modifications are unlikely because even simple mutations in the H-2 antigen completely block the cytotoxic reaction[57]. Recent experiments in which the neoantigen was added externally in the form of an inactivated Sendai virus[58] also largely ruled out a direct chemical modification of the H-2 antigen by the neoantigen.

Molecular associations on the cell surface can be studied with the simple experimental technique of "cocapping" (see Ref.[59] and Figs. 4 and 5). Antibodies coupled to a fluorescent dye are used to specifically label certain cell surface antigens. After a few minutes, patching occurs on the cell surface by passive diffusion. If the cells are incubated for a further 15–30 min at 37 °C, the small, fluorescently labeled aggregates slowly cap at one pole of the cell. If one wants to see whether another molecule is also moved during this process, a second fluorescently labeled antibody directed against this molecule must be added. After capping of the first antigen, the second antigen is either diffusely distributed over the cell surface or is at the same pole of the cell as the first antigen. Simultaneous observations of this type are made possible by the fact that the two antibodies are coupled to different fluorescent dyes which can be distinguished by suitable choice of filters and the wavelength of the ultraviolet light (Fig. 4).

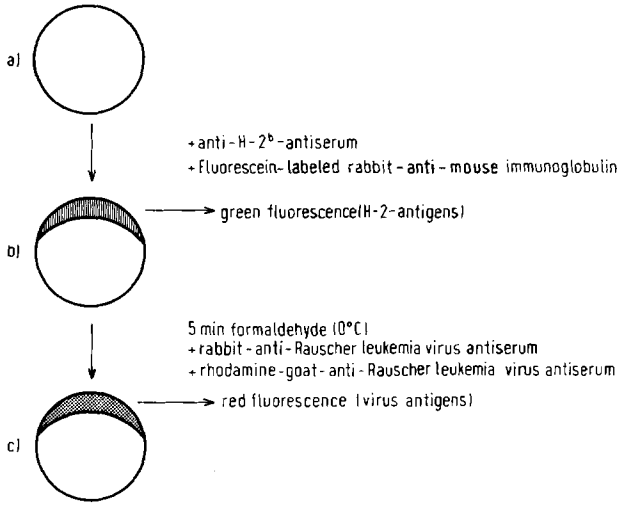


Fig. 4. Experimental scheme for inducing "cocapping" of H-2 antigens and leukemia virus antigens in mouse leukemia cells. a) Mouse lymphoma cells (H-2^b) infected with leukemia virus; b) H-2 antigens at one pole of the cell after capping; c) virus antigens in the same position as the H-2 antigens after cocapping.

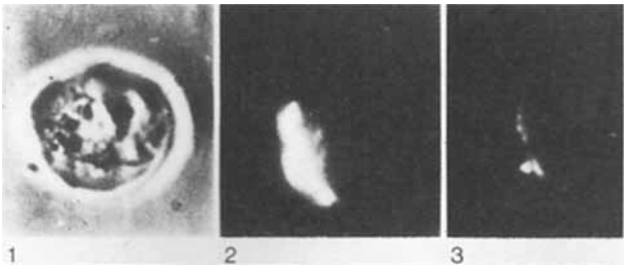


Fig. 5. Cocapping of H-2 antigens and leukemia virus antigens (see also Fig. 4). 1. Phase contrast photograph of a mouse leukemia cell (EL 4). 2. "Capping" of H-2 antigens (visualized by immunofluorescence (fluorescein). 3. "Cocapping" of leukemia virus antigens (visualized with rhodamine coupled antibodies). Results taken from Ref. [48].

The following problem has been investigated with this experimental procedure—do virus antigens (*e.g.* mouse leukemia virus glycoprotein gp 69/71) cocap after capping of H-2 antigens in type H-2^b mouse lymphoma cells (*e.g.* EL-4 cells),

or are they diffusely distributed over the cell surface? In almost every case virus antigens were cocapped with H-2 antigens[48]. An example is shown in Figure 5. Similar findings were obtained[62] with another serological method—the "lysostrip" technique[60,61]. Although both types of results are no direct evidence for the formation of an antigen-virus antigen hybrid complex, they can however be used for a working hypothesis (Fig. 6).

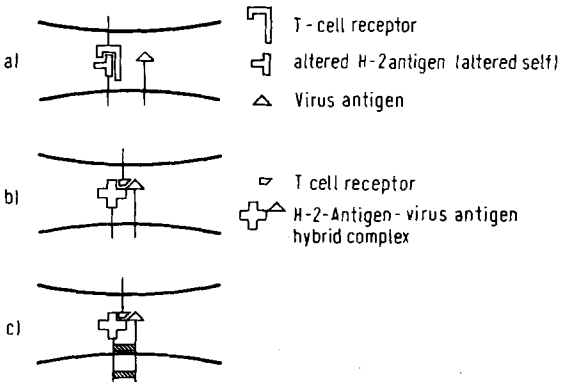


Fig. 6. One-receptor models for the immune surveillance of virus-infected cells or tumor cells by cytotoxic lymphocytes. Presentation of the participation of histocompatibility antigens. a) Cytotoxic lymphocytes (killer cells) possess one receptor which recognizes an H-2 antigen modified by the neoantigen ("altered self"). b) A T cell receptor recognizes a hybrid formed from H-2 and virus antigens by protein interactions. c) As b) but additional contractile proteins lying above or below the cell surface are necessary.

It is not easy to describe the chemical and physical basis of molecular associations of this type. Do stoichiometric ratios have to be presumed (*i.e.* complexes made up of one H-2 antigen and one virus antigen) or can larger, non-stoichiometric molecular associations between the two antigens be expected? If only 1:1 complexes exist, each of the two molecules should possess one specific, monovalent binding site which does not permit any further linkages. If the H-2 antigens have a strong tendency to associate with other proteins, then they will form molecular complexes with many different cell surface proteins (*e.g.* with weak histocompatibility antigens[51,52] and the product of the Y gene[53]). In the case of a multispecific binding site the degree of association between the H-2 and virus antigens as observed in the "cocapping" and "lysostrip" experiments would be extremely high.

The results of the "cocapping" and "lysostrip" experiments can, however, also be accounted for by special binding properties of the virus proteins. For functional reasons virus proteins have a high capacity for adsorbing onto cell surface proteins and could therefore also form molecular complexes with H-2 antigens in the cell membrane. In this case, the extent of H-2 antigen-virus antigen hybrid complex formation as observed in the cocapping experiments would not be necessary for the cytotoxic reaction. However, the interpretation of these findings with regard to the mechanism for the cytotoxic reaction would be correct. It is known that H-2 antigens do not build such strong molecular complexes with other cell surface antigens which have been studied. H-2 antigens do not form complexes amongst themselves, neither are they associated with immunoglobulins or Ia antigens as has been shown in "cocapping" and "lysostrip" experiments[17,48,61–63].

No currently known experiments allow a definite decision to be made in favor of a single receptor model of the recognition and elimination of abnormal cells by cytotoxic lymphocytes.

3.4. "Killer" Cells with Two Receptors for the Destruction of Target Cells

In this model (Fig. 7a), the cytotoxic lymphocyte possesses two receptors: one which specifically recognizes H-2 antigens (H-2 receptor) and another for neoantigen. The H-2 receptor can be genetically determined on a similar basis as the products of the H-2K and H-2D loci. Furthermore, a mouse must always have a stock of cells which have receptors for all H-2 antigen types. Those H-2 receptors which recognize syngeneic H-2 antigens must be selected by special tolerance mechanisms so that they can recognize very slight differences from the individual's cells. The neoantigen receptor needs a high degree of polymorphism in order to recognize a large number of different antigens.

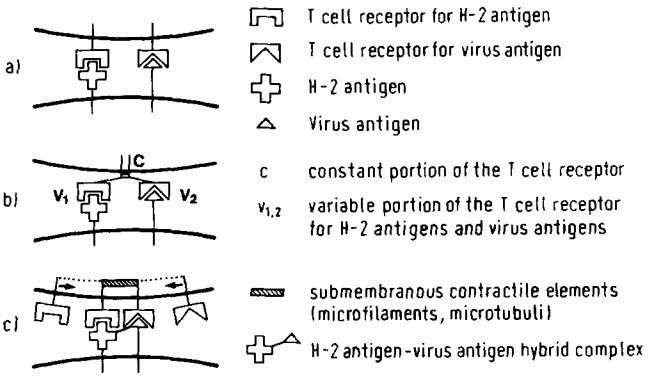


Fig. 7. Two-receptor models for the immune surveillance of virus-infected cells or tumor cells by cytotoxic lymphocytes. Representation of the participation of histocompatibility antigens. a) Cytotoxic lymphocytes ("killer" cells) possess two genetically separately coded receptors for H-2 antigens and neoantigens. b) Cytotoxic lymphocytes have a bivalent disulfide linked immunoglobulin-like receptor with two different variable regions and two possibly identical constant regions. c) Two receptors as in a); the two receptors can be drawn together by a hybrid complex and thus trigger signals for cell division and differentiation of T lymphocytes (see also Ref. [68]).

With the introduction of a second receptor system, a problem arises which initially seems to contradict a two receptor model. According to the known serological and cell immunological findings, the two receptors must both be present on the same cytotoxic cell. This was shown by using simultaneously cytotoxic T cells directed against either the H-2 antigens or the neoantigen. Cytotoxicity against the desired target cell (having a defined H-2 antigen and a defined neoantigen) could not be produced by mixing these two types of T cells. The frequency expected for a clonal distribution of two polymorphic receptors on the same cell should be sufficiently high to initiate a cellular immune response. Since the statistical probability of two heterogeneous receptors on one cell is low, a two-receptor model in this form still involves many problems.

It can easily be imagined from this large number of arguments how confused the situation still is at the present time. Although serological and cell immunological experiments have recently been greatly improved, and several combinations have

been tested, little progress is being made in present discussions (for summaries see Ref. [64]). Significant progress can only be expected either when direct evidence is obtained for the formation of an H-2-antigen-virus-antigen hybrid complex, or when two types of T cell receptors can be demonstrated on the same cell. Very elegant and promising experiments have been reported by two laboratories which seem to characterize at least one T cell receptor in molecular terms[65, 66]. It appears to be an immunoglobulin-like molecule consisting of two disulfide linked polypeptide chains ($M_r = 72000$) with a variable region (V_H) as in normal immunoglobulins (see Figs. 7b and 7c).

4. Implications and Applications

Attempts to combine the results of chemical structural analyses and the biological observations of H-2 antigens do not yet yield a comprehensive picture. The most important recent results can be easily summarized by considering structure and function in isolation from each another.

As far as structure is concerned, the current state of knowledge allows one to postulate a molecular model as a working hypothesis. This model describes the number of subunits, their interactions and their orientation on the cell surface. Furthermore, sequence analyses demonstrate genetic relationships between the K and D products with the histocompatibility antigens of other species (man) and even with immunoglobulins. In order to derive structural rules one needs the total amino acid sequence of the heavy chains of the histocompatibility antigens. Only by this approach can the localization of the antigenic determinants and the molecular principles of polymorphism be elucidated.

Knowledge of the primary structure of β_2-microglobulin revealed evolutionary relationships to immunoglobulins. This has not led to any progress with regard to the function of the histocompatibility antigens. It is open to discussion whether β_2-microglobulin could be a general acceptor for a T cell receptor. It is conceivable that the T cell receptor has a constant binding site (C region) for the β_2-microglobulin and a variable region (V region) for the antigenic site on the heavy chain of the H antigen or the antigenic determinant of a hybrid complex. On the other hand, β_2-microglobulin could also bind a complement component to trigger the disintegration of the target cell[67].

In 1959 *Thomas*[68] wrote that nature had not invented H antigens in order to make the life of the transplant surgeon difficult. Recent results show that the rejection of foreign cells and the elimination of the body's own abnormal cells are subject to similar rules. The examples of abnormal cells cited (virus-infected cells, tumor cells) appear so frequently during the long lifetime of a vertebrate organism and their effects are so strong that a pressure for an evolutionary selection to create and maintain such a defense system seems to be justified. This system seems to have developed from rejection systems of simple multicellular organisms. In sponges, for example, a high degree of specificity in cell-cell contact has been shown. In organisms of this type which live closely packed together in a confined environment, this principle is extremely important for the preservation of biological individuality. In addition, transplantation immunity including memory effects has been demonstrated in simple multicellular organisms such as corals[38]. In vertebrates the danger lies not so much in the mixing of cells from different individuals, but rather in the alteration of the cells within one organism by virus infections, tumor formation and somatic mutations. A teleological basis for the presence and functioning of such a system can be easily imagined.

The discussion as to whether a one- or two-receptor model operates in T lymphocytes may end in a compromise. Firstly, there could be two types of variable gene products which are clonally distributed on the T cells. The first variable gene product, the H-2 antigen receptor, is very strongly selected for the recognition of syngeneic H-2 products. The number of clones needed for H-2 recognition is thus greatly reduced. The statistical problems involved in the existence of two variable receptors on one cell would then be easier to resolve. However, the second variable gene product, the neoantigen receptor, still requires a broad diversity.

Secondly, it can be argued that two variable receptor proteins are linked together in the form of two subunits in a bivalent receptor (Fig. 7b). A bivalent T cell receptor of this type would also explain the unresolved problem of the molecular association between H antigens and neoantigens, since the T cell receptor itself produces this association. In this model it would be very easy to imagine the function of the β_2-microglobulin as being that of a contact protein for a T cell receptor.

Thirdly, two variable but physically separate T cell receptors can be pulled together by submembranous contractile elements as a result of binding to an H-2 antigen-neoantigen hybrid complex on the surface of the target cell (Fig. 7c). This process could trigger a signal which initiates the proliferation of the competent T cell. The triggering of signals for cell division and differentiation of lymphocytes by the binding of extracellular substances to cell surface proteins is already known in several systems[69].

Most of the current serological and cell immunological findings as well as the "cocapping" and "lysostrip" experiments outlined above point rather to a one-receptor model.

The immune defense system has reached a high degree of complexity. In such complex systems the susceptibility to errors increases rapidly. The control of errors and quality is only satisfactorily effective if all elements of the system are intact. In this respect the immune system resembles the central nervous system which compensates for the loss of active elements in the aging process with memory cells. This principle operates very effectively in common bacterial and viral infections. In old age, tumor cell transformations are perhaps no longer recognized with certainty because of the absence of competent memory cells and the much less frequent formation of tumor cells. No further evolutionary progress can be expected because reproduction stops in old age and the present increase in life-span no longer affects selection.

The experiments described above and their discussion make it clear that neither chemistry nor biology can answer the most important questions concerning this area of research. The medical importance of histocompatibility antigens has so far been limited mainly to the problems of organ transfer. Long term successes have only been achieved in special cases (*e.g.* in kidney transplantations). The understanding of the functions of the histocompatibility antigens in the immune

surveillance of abnormal cells is not sufficient to develop a therapy which makes active use of the immune surveillance system. With precise molecular data it will be possible to use biological methods to successfully deal with diseases due to defective regulatory cell mechanisms. Chronic viral diseases and associated defective defense reactions (*e.g.* possibly multiple sclerosis and cancer) belong to this category. A new type of immunotherapy will perhaps soon be possible by using killer cells cultured *in vitro* which are specifically directed against individual cancer cells. After the great success of chemically and bacteriologically synthesized drugs this could be the beginning of an era of scientifically based cell therapy.

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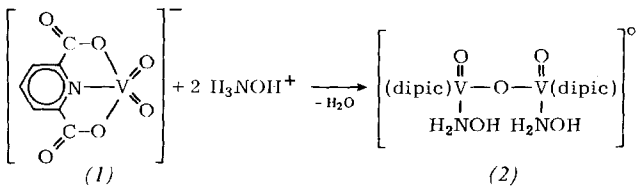
Communications are brief preliminary reports of research work in all areas of chemistry which, on account of its fundamental significance, novelty, or general applicability, should be of interest to a broad spectrum of chemists. Authors of communications are requested to state reasons of this kind justifying publication on submission of their manuscript. The same reasons should be clearly apparent from the manuscript. In cases where the editorial staff decide, after due consultation with independent referees, that these conditions are not met, manuscripts will be returned to the authors with the request to submit them for publication in a specialist journal catering for scientists working in the field concerned.

Dipicolinato(hydroxylamido-*O*,*N*)(nitrosyl)aqua-vanadate—A Nitrosyl Complex of Vanadium with "side on" Coordinated Hydroxylamine[**]

By *Karl Wieghardt*, *Udo Quilitzsch*, *Bernhard Nuber*, and *Johannes Weiss*[*]

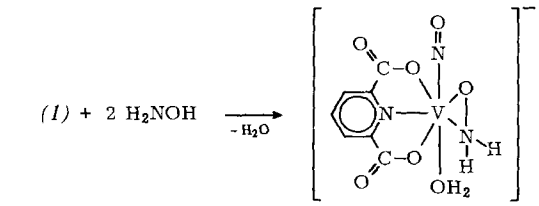
Vanadium(V) undergoes reduction with hydroxylamine in alkaline or acidic aqueous solution; depending upon the reaction conditions N_2, N_2O, and NO (as well as NH_3) may be formed[1]. A vanadium(V)-hydroxylamine 1:1 complex has been shown to exist in acidic solution[2] but so far has not been isolated.

Reaction of five-coordinated *cis*-dioxo(dipicolinato)vanadate(V) ion *(1)*[3] with hydroxylammonium chloride in weakly acidic solution (25 °C) affords a colorless neutral complex *(2)*, which on the basis of its analytical and IR spectroscopic data can be formulated as μ-oxo-bis[oxo(dipicolinato)(hydroxylamine-*N*)vanadium(V)].



(1) *(2)*

In alkaline solution *(1)* reacts quantitatively with hydroxylamine (1:2) without evolution of gas (!) to give deep-red solutions. Addition of solid KCl or CsCl yields air stable crystalline potassium and cesium salts, respectively. The IR spectra of these salts show the characteristic bands of the coordinated dipicolinato ligand (dipic)[3] and a strong band at 1530 cm^{-1} which we assign to a ν(N=O) vibration.



(3)

The structure of the anion *(3)* was determined by X-ray spectroscopy (Fig. 1). $Cs[V(dipic)(H_2NO)(NO)(H_2O)]\cdot 2H_2O$ crystallizes in the orthorhombic space group D_{2h}^{11}-Pcmb with $a = 839.4(3)$, $b = 884.3(2)$, $c = 1936.1(6)$ pm, $Z = 8$. Refinement with structure factors of 1260 observed independent reflections $[I > 2.58\sigma(I)]$ converged to an unweighted R value of 5.9 %. The positions of the H atoms could not be determined because of the poor quality of the crystals (platelets).

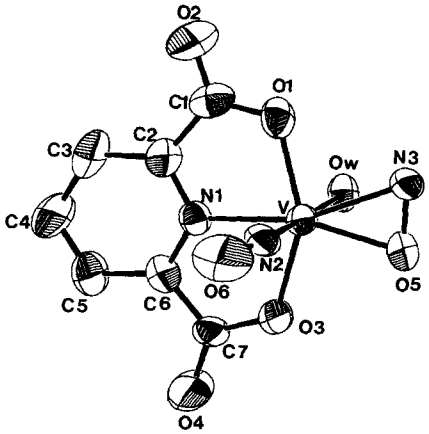


Fig. 1. Structure of the complex anion *(3)* in $Cs[V(dipic)(H_2NO)(NO)(H_2O)]\cdot 2H_2O$ (without H atoms). Important bond lengths [pm] and angles [°]:

V—N1	211.0(14)	V—O1	207.9(17)	N2—O6	119.6(23)
V—N2	169.3(17)	V—O3	210.5(14)	N3—O5	141.7(26)
V—N3	205.4(17)	V—O5	201.5(12)	V—Ow	217.2(16)

V—N2—O6	175.7(16)	N2—V—Ow	178.0(8)
N3—V—O5	40.7(7)	O1—V—O3	148.4(5)
V—N3—O5	68.1(8)	V—O5—N3	71.1(9)

The central vanadium atom is surrounded by a distorted pentagonal-bipyramidal array of tridentate dipicolinate ligands, a bidentate hydroxylamido ligand and—in the axial positions—a nitrosyl and an aqua ligand (the formal coordination number is 7) (Fig. 1). The hydroxylamido ligand is most probably coordinated as $H_2N—O^-$[5]. The nitrosyl group is almost linearly coordinated, and the V—N2 bond length is relatively short. Analogous bonding has been reported for the $[V(CN)_6NO]^{4-}$ ion[4]. The H_2NO^- ligand is coordinated "side on" *via* the O- and the N-atom, the N3—O5 distance corresponds to that of the usual N—O single bond length.

The smooth reaction course in alkaline medium and the lack of formation of gaseous reaction products are considered to be indicative of an intramolecular transfer of two electrons from *N*-coordinated hydroxylamine to V^V (formally, V^{III} and $NO^{\ominus}$ are formed). This is supported by the following experiment: Reaction of the V^{III}-complex *(4)* with hydroxylamine in alkaline solution likewise affords *(3)*:

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Prof. *H. Hartkamp*, Gesamthochschule Wuppertal, for valuable discussions.

$$[(\text{dipic})\text{V}(\text{OH}_2)_3]^+ + 3\ \text{H}_2\text{NOH} + 2\ \text{OH}^- \longrightarrow (3) + \text{NH}_3 + 5\ \text{H}_2\text{O}$$
(4)

However, in this case NH_3 is also formed, for the $NO^{\ominus}$ ligand must now be formed by disproportionation of the hydroxylamine to ammonia and hyponitrous acid.

Procedure

(2)·H_2O: $[H_3NOH]Cl$ (2.8 g) is added in small amounts to a solution of $Cs[V(O)_2(dipic)]\cdot H_2O$[3] (8 g) in 100 ml water (25 °C). A colorless, crystalline precipitate is formed, which is separated by filtration and washed with alcohol and ether (5.1 g).—The IR and Raman spectra show an intense ν(V=O) band at 980 cm^{-1}.

K*(3)*·3H_2O: A solution of $[H_3NOH]Cl$ (1.2 g) and KOH (2.4 g) in water (10 ml) is added to a solution of $K[V(O)_2(dipic)]$[3] in water (30 ml). The mixture becomes dark-red in color on warming (40 °C). After 15 h at 2 °C orange-colored crystals are filtered off and washed with alcohol and ether (3 g).—The cesium salt can be precipitated as red crystals by treatment of an aqueous solution of the potassium salt with solid CsCl.

*(4)*Cl·2H_2O: An aqueous suspension (30 ml) of pyridine-2,6-dicarboxylic acid (3.5 g) and vanadium trichloride (3.1 g) is treated with 15 ml conc. HCl and heated to 50 °C. Complete dissolution of the violet suspension takes place, giving a dark green solution. On cooling to 5 °C yellow crystals of the desired product precipitate which are filtered off and washed with alcohol and ether (5 g).

All the complexes gave correct elemental analyses [V, C, H, N (K, Cs, Cl)].

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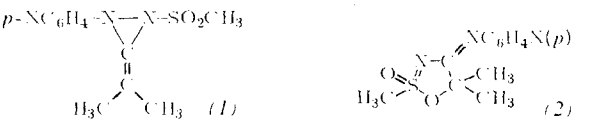
CAS Registry numbers:
Cs*(1)*, 66225-05-6; K*(1)*, 66225-00-1; *(2)*, 66225-04-5; Cs*(3)*·2H_2O, 66225-02-3; K*(3)*, 66225-03-4; *(4)* Cl, 66225-01-2; $[H_3NOH]Cl$, 5470-71-1

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Reactions of Methanesulfonyl Azide with Ketenimines (a Revision)[**]

By *Gerrit L'abbé, Chih-Chou Yu, Jean Paul Declercq, Gabriel Germain*, and *Maurice Van Meerssche*[*]

In a previous article, two of us reported that *N*-aryldimethylketenimines react with methanesulfonyl azide at room temperature to give products which were characterized as alkylidenediaziridines *(1)*[1].



(a), X = H; *(b)*, X = CH_3; *(c)*, X = Br

However, X-ray diffraction analysis of the product with X = CH_3 has shown that our compounds are in fact 4-arylimino-2,5,5-trimethyl-4,5-dihydro-1,2λ⁶,3-oxathiazol-2-ones *(2)* (Fig. 1).

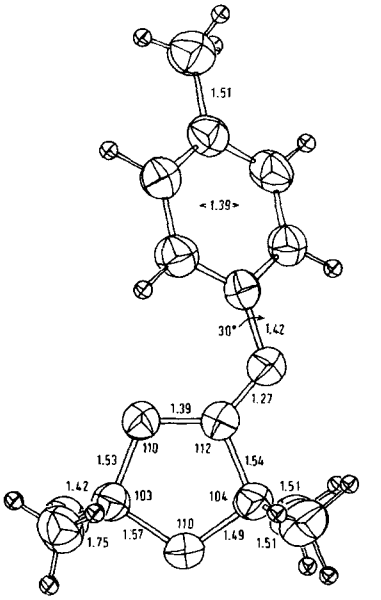
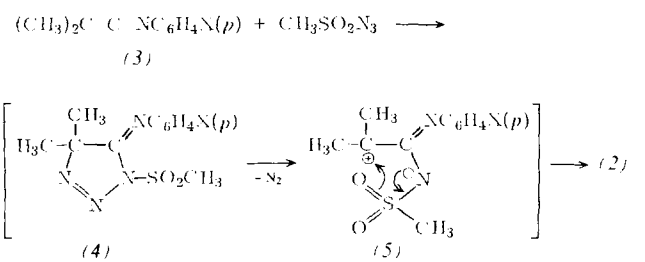


Fig. 1. Molecular structure of *(2b)* with the important bond lengths [Å] and angles [degrees]. The oxathiazoline ring is planar. Compound *(2b)* crystallizes monoclinically in space group $P2_1/a$ with $a = 32.057$, $b = 5.764$, $c = 7.039$ Å; $\beta = 96.49°$; $Z = 4$. The structure was solved by the MULTAN 77 program [2a] and refined with the X RAY 72 system [2b] to $R = 0.043$ for 1361 reflections (SYNTEX $P2_1$ diffractometer; $Mo_{K\alpha}$ radiation, $2\theta_{max} = 47°$).

The spectroscopic properties of this unusual ring system[3] are compatible with structure *(2)* [IR (KBr): *ca.* 1640 ($\nu_{C=N}$), 1290, 1160 and 1050 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.7$ and 1.8 ($2CH_3$ at C-5); ^{13}C-NMR ($CDCl_3$) of *(2a)*: $\delta = 98$ and 162 (C-5 and C-4 in the hetero ring), 149, 123, 124 (C-1, C-2, and C-4 in the phenyl ring)[4]; MS $[M - CH_3SO_2]^+$ and $[CH_3SO_2]^+$ as intense signals].

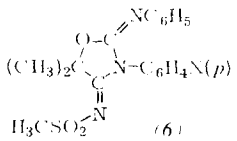


(3) *(4)* *(5)*

Mechanistically, the reaction probably involves triazoline *(4)*[5,6] and the zwitterion *(5)*. Although this mode of decomposition is known for acyl azides[7], it is without precedent for sulfonyl azides[5]. The possible intermediacy of a nitrene is completely excluded on the basis of the mild reaction conditions (room temperature).

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(6)

In our previous publication, we have also reported that the compounds now to be considered as *(2)* react with phenyl isocyanate. X-ray analysis[8] of compound *(6b)* confirmed our original assignment.

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CAS Registry numbers:
(1a), 62962-27-0; *(1b)*, 62962-28-1; *(2a)*, 66255-49-0; *(2b)*, 66255-50-3; *(6b)*, 62962-34-9; methanesulfonyl azide, 1516-70-7

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[8] *(6b)*: monoclinic, $a = 23.962$, $b = 12.414$, $c = 13.348$ Å; $\beta = 103.69°$; space group C2/c, $Z = 8$. Refinement to $R = 0.117$ for 1340 reflections (SYNTEX $P2_1$ diffractometer, $Mo_{K\alpha}$ radiation, $2\theta_{max} = 47°$).

Catalytic Allylation of Phenylhydrazones[**]

By *Ugo Bersellini, Gian Paolo Chiusoli*, and *Giuseppe Salerno*[*]

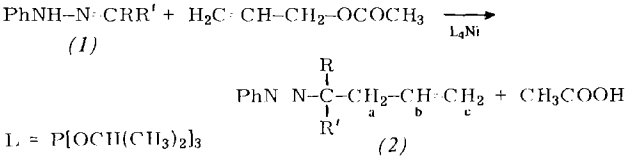
During the course of our studies on insertion reactions into transition metal-carbon bonds[1] we found that allylnickel complexes, formed *in situ* by the oxidative addition of an allylic ester to nickel(0), are particularly effective for the insertion of chelated double bonds[2] and alkynes[3] into certain transition metal-carbon bonds. Substituted hydrazones have recently been reported to react with dienes in the presence of nickel or palladium complexes to give alkylation products at the carbon or the nitrogen[4, 5]. Although bis(π-allyl)nickel or palladium are probably the intermediates, reaction of hydrazones with allylnickel halides give only low yields of *N*-alkyl derivatives. We observed, however, that phenylhydrazones *(1)* react catalytically with allylic acetates in THF (at reflux under nitrogen) to give azo compounds *(2)* (formulated here for the simplest allyl compound). Examples are listed in Table 1.

Phenylhydrazones of both aldehydes and ketones appear to be reactive. Benzophenone, however, is practically unreactive probably for steric reasons. Table 1 reports yield and turn-over numbers (molecules of azo derivatives formed per molecule of nickel complex).

Yields and turn-over numbers drop to lower values on passing to higher homologs of the allylic groups. Thus, reaction of 2-butenyl acetate with formaldehyde *N*-phenylhydrazone *(1a)* affords *(3a)* in 20% yield only (turn-over

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(1) (2)

Table 1. Reaction of phenylhydrazones *(1)* (1 mmol) with allyl acetate (1 mmol) in THF (10 ml) to give azo compounds *(2)*; catalyst: tetrakis(triisopropyl phosphite)nickel(0) (0.05 mmol); 70°C, 15 h.

	R	R'	Yield [a] [%]	mol *(2)*/mol L_4Ni
(a)	H	H	51.0	10.2
(b)	H	C_6H_5	62.5	12.5
(c)	H	*n*-C_4H_9	58.5	11.7
(d)	—$(CH_2)_5$—		51.0	10.2
(e)	CH_3	CH_3	35.0	7.0

[a] Based on phenylhydrazone *(1)* employed; unconverted *(1)* was recovered almost completely except in the case of *(1a)* (75%).

number = 2). Interestingly, the branched isomer is formed selectively (98%) instead of the linear one.

$$PhN{=}N{-}CH_2{-}CH(CH_3){-}CH{=}CH_2 \quad (3a)$$
$$\qquad\quad a \qquad\quad b \quad c$$

Other donor solvents behave in the same way as THF. In toluene or hexane however, *N*-substitution products of type *(4)* predominate (formulated for allyl acetate).

$$RR'C{=}N{-}N(Ph){-}CH_2{-}CH{=}CH_2 \quad (4)$$

On using tetrakis(triphenylphosphane)nickel(0) in toluene, *C*-alkylated products are formed, but the reaction loses its catalytic character.

When tetrakis(triphenylphosphane)palladium(0) is used instead of the nickel complexes, the catalytic attack at the nitrogen predominates. Thus, reaction of 40 mol of formaldehyde *N*-phenylhydrazone *(1a)* and 40 mol of allyl acetate per mol of Pd complex in THF (75°C, 20 h) affords *(4a)*, R = R' = H, in 68% yield (turn-over number 27).

Ligand and substrate effects were studied on the nickel complexes under the conditions set out in Table 1. An excess of phenylhydrazone *(1)* leads to an enhanced catalytic effect, the number of molecules of product per molecule of nickel complex varying from 1.9 to 7.7 on passing from an excess of 5 to one of 12 mol of formaldehyde *N*-phenylhydrazone *(1a)* per mol of nickel complex. The corresponding yield increases from 38.0 to 64.2%, but begins to drop to lower values (51%) if a higher excess of phenylhydrazone (20 mol *(1a)*/mol L_4Ni) is used, while the catalytic effect continues to improve (see Table 1). If, however, an excess of triisopropyl phosphite is used (40 mol/mol L_4Ni) the yield does not decrease any more and 25 mol *(2a)*/mol L_4Ni are obtained (excess of *(1a)* 50 mol/mol L_4Ni).

An analogous tendency was observed with acetone *N*-phenylhydrazone *(1e)*. Thus the phosphite in excess helps to maintain the catalytic cycle. The series of decreasing efficiency of ligands appears to be the following: triisopropyl phosphite ≃ diisopropoxy(phenyl)phosphane > triethyl phosphite > trimethyl phosphite ≃ triphenyl phosphite > triphenylphosphane.

Experimental

Allyl acetate and phenylhydrazone *(1)* (prepared and stored under nitrogen) are dissolved in THF or in other ethereal

or amidic solvents and placed in a Schlenck tube under nitrogen together with tetrakis(phosphite) nickel complexes. After warming at 70°C for several hours with stirring, the products *(2)* are separated by distillation, chromatographed and identified by elemental analysis, mass spectrum, and IR and ^{1}H-NMR spectra (Table 2).

Table 2. Characteristic ^{1}H-NMR data of compounds *(2a)*—*(2e)* and *(3a)* [in $CDCl_3$, TMS int.; a, b, c see formulas *(2)* and *(3)*].

(2a), δ = 2.6 (q, J = 7 Hz, $2H_a$), 4.1 (t, J = 7 Hz, 2 homoallyl. H), 4.85—5.25 (m, $2H_c$), 5.5—6.2 (m, $1H_b$)
(2b), δ = 2.8 (t, $2H_a$), 4.5—5.2 (m, 1 benzyl. H), 4.5—5.2 (m, $2H_c$), 5.3—5.9 (m, $1H_b$)
(2c), δ = 0.9—1.5 (br., 7H, $CH_3(CH_2)_2$), 1.7—1.9 (br., CH_2 of R'), 2.5 (t, J = 7 Hz, $2H_a$), 3.6 (m, J = 7 Hz, 1 homoallyl. H), 4.7—5.15 (m, $2H_c$), 5.3—6.0 (m, $1H_b$)
(2d), δ = 1.3—2.5 (br., 10H of R and R'), 2.4 (d, J = 7 Hz, $2H_a$), 4.7—5.1 (m, $2H_c$), 5.3—5.9 (m, $1H_b$)
(2e), δ = 1.2 (br. s, $2CH_3$), 2.4 (d, J = 7 Hz, $2H_a$), 4.7—5.2 (m, $2H_c$), 5.35—6.0 (m, $1H_b$)
(3a), δ = 1.1 (d, J = 7 Hz, CH_3), 2.8 (m, $1H_a$), 3.85 (dd, J = 7 Hz, J' = 1.5 Hz, 2 homoallyl. H), 4.8—5.2 (m, $2H_c$), 5.35—6.2 (m, $1H_b$)

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CAS Registry numbers:
(1a), 6228-40-6; *(1b)*, 588-64-7; *(1c)*, 6228-43-9; *(1d)*, 946-82-7; *(1e)*, 103-02-6; *(2a)*, 66255-55-8; *(2b)*, 66255-56-9; *(2c)*, 66255-57-0; *(2d)*, 66255-58-1; *(2e)*, 66255-59-2; *(3a)*, 66255-60-5; *(4a)*, 66255-61-6

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[2] *G. P. Chiusoli, G. Salerno, F. Dallatomasina*, J. Chem. Soc. Chem. Commun. *1977*, 793.
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formula $Cs_4[Nb_4O_{12}]$ in which Nb^{5+} exhibits coordination number (C.N.) 5 towards O^{2-}[2].

Since literature data on the properties of $RbTaO_3$[3] undoubtedly warranted re-examination and it was questionable regarding the still unknown structure whether a perovskite variant with C.N. 6 exists—as previously suggested[4]—or a structure analogous to that of $CsNbO_3$ with C.N. 5 were more likely, we have prepared single crystals of $RbTaO_3$ [intimate mixture of $RbO_{0.65}$ with Ta_2O_5 (Merck analytical grade). Rb:Ta = 1.05:1; sealed Ni bomb, 1000°C, 21 d] in the form of water-clear thin platelets.

Crystals of $RbTaO_3$ are monoclinic with $a = 9.58_9$, $b = 8.50_5$, $c = 8.13_5$ Å, $\beta = 94.8_7°$ in C2/m; $d_X = 6.32$, $d_{pyc} = 6.37$ g·cm^{-3}. Diffraction data were collected using a four-circle automatic diffractometer [PW1100, $4° \leq \theta \leq 33°$, Mo-Kα], and the structure was determined using Patterson, Fourier, and least-squares techniques. For 1014 of the 1296 *hkl* data $R = 9.9\%$ (with no correction being made for the marked absorption due to the platelet shape of the crystal). The atomic positional and thermal parameters of the anisotropic refinement (O^{2-} isotropic) along with their standard deviations are listed in Table 1.

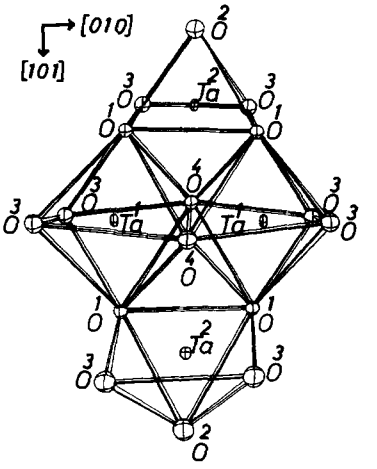


Fig. 1. Perspective diagram of the constituent structural groups $[Ta_4O_{8/1}O_{8/2}]$ in $RbTaO_3$.

Table 1. Atomic positional and thermal parameters of $RbTaO_3$ (standard deviations in brackets).

Atom	Position	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Rb^1	4i	0.1630(4)	0.5	0.2440(5)	0.015(2)	0.011(2)	0.012(2)	0.0	0.003(1)	0.0
Rb^2	4h	0.0	0.2305(7)	0.5	0.061(4)	0.023(3)	0.027(3)	0.0	0.025(3)	0.0
Ta^1	4g	0.0	0.1903(2)	0.0	0.0032(8)	0.0022(8)	0.0155(9)	0.0	0.0011(5)	0.0
Ta^2	4i	0.2409(2)	0.5	0.8051(2)	0.0062(8)	0.0041(8)	0.0092(8)	0.0	−0.0008(6)	0.0
O^1	8j	0.119(2)	0.166(2)	0.210(2)	0.004(3)					
O^2	4i	0.173(3)	0.5	0.591(4)	0.015(6)					
O^3	8j	0.113(2)	0.342(3)	0.896(3)	0.016(5)					
O^4	4i	0.379(4)	0.5	0.049(4)	0.018(7)					

The isotropic temperature factor is defined as: $\exp[-8\pi^2 V \sin^2\theta/\lambda^2]$,

the anisotropic as: $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^*c^* + 2U_{13}hla^*c^* + 2U_{12}hka^*b^*)]$

Coordination Number 5 and 6 in $RbTaO_3$: $Rb_{4\infty}^2[Ta_4O_{12}]$[1]

By *Michael Serafin* and *Rudolf Hoppe*[*]

In a structural analysis of $CsNbO_3$, we unexpectedly found isolated cluster-like structural units commensurate with the

A complex layer structure is present:

Primary structure: Ta^1 is surrounded by a distorted octahedral array of six oxygen atoms [Ta—O = 1.92_6 (2×), 1.98_3 (2×), 2.05_0 (2×) Å], and Ta^2 by a distorted tetragonal-pyramidal arrangement of five O atoms [1.80_7 Å; 1.96_0 (2×), 2.00_3 (2×) Å].

Secondary structure: groups containing two Ta^1 atoms and two Ta^2 atoms bonded *via* common oxygens and the two coordination octahedra of Ta^1 linked together *via* a common pair of O^4 atoms; of the four O^1 atoms each adjacent pair

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forms a basal edge of one of the two pyramids, which in turn joins the pyramid to the two octahedra (see Fig. 1). O^2, as apex of a pyramid, belongs only to Ta^2. O^3 atoms, occupying the two remaining corner points of each of the mentioned coordination polyhedra, complete the secondary structural unit.

Tertiary structure: Four O^3 atoms, as $O_{8/2}$, couple the Ta_4O_{12} groups mentioned previously in accordance with the formula $[\{(O^4_{2/2}Ta^1)_2O^1_4(Ta^2O^2_{1/1})_2\}O^3_{8/2}]$ such that Ta^1 of one of the Ta_4O_{12} units is connected by O^3 with Ta^2 of one of the other units and *vice versa*. Each of the groups is coupled *via* two O^3 atoms with a total of four other groups such that a strongly puckered layer is formed.

Quaternary structure: Identical layers of the above type are stacked in the [001] direction, translated by length *c*.

An unusual difference is observed in the coordination of the two crystallographically different Rb atoms: Rb^1, with C.N. 8 [2.71_4, 2.81_6; and 2.88_2 (2×), 3.09_8 (2×), and 3.13_4 (2×) Å] couples the apex of a pyramid of one group with four groups of another layer; Rb^2, with C.N. 4 [2.76_1 (2×), 2.88_9 (2×) Å], on the other hand, couples two groups each of two layers in a quasi-tetrahedral arrangement. Two each of these tetrahedra have a common edge.

We have calculated the Madelung part of the lattice energy (MAPLE[5]) of $RbTaO_3$ [4815 kcal/mol] and compared it with MAPLE values for other oxotantalates, since the structure of Ta_2O_5 is still uncertain. The comparison shows that the value obtained by difference [9057 kcal/mol] for Ta_2O_5 from MAPLE ($RbTaO_3$) is equal to the mean value [9055 kcal/mol] obtained for Ta_2O_5 from other oxotantalates.

$RbTaO_3$ hydrolyzes immediately on exposure to water. Previous reports of solubility data of $RbTaO_3$ are thus incorrect[6].

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CAS Registry number:
$RbTaO_3$, 12333-74-3

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Extremely High Electronegativities[**]

By *Dieter Lentz* and *Konrad Seppelt*[*]

It would appear inconceivable for an atom present in a molecule to have an electronegativity greater than that of a fluorine atom. And yet studies on compounds containing $OSeF_5$ and $OTeF_5$ ligands[1] have led us to the conclusion that these groups actually do have higher electronegativity values than fluorine, at least in the sense of the electron pair repulsion model (VSEPR theory)[2].

IF_5 reacts with the ligand transfer agent $B(OTeF_5)_3$ to give $FI(OTeF_5)_4$ with retention of the square-pyramidal molecular structure, the remaining fluorine atom occupying the axial position [eq. (1)]. Attempts to accomplish complete substitution were unsuccessful [eq. (2)]. The completely substituted species $I(OTeF_5)_5$ could only be obtained by oxidation of $I(OTeF_5)_3$[3] [eq. (3)].

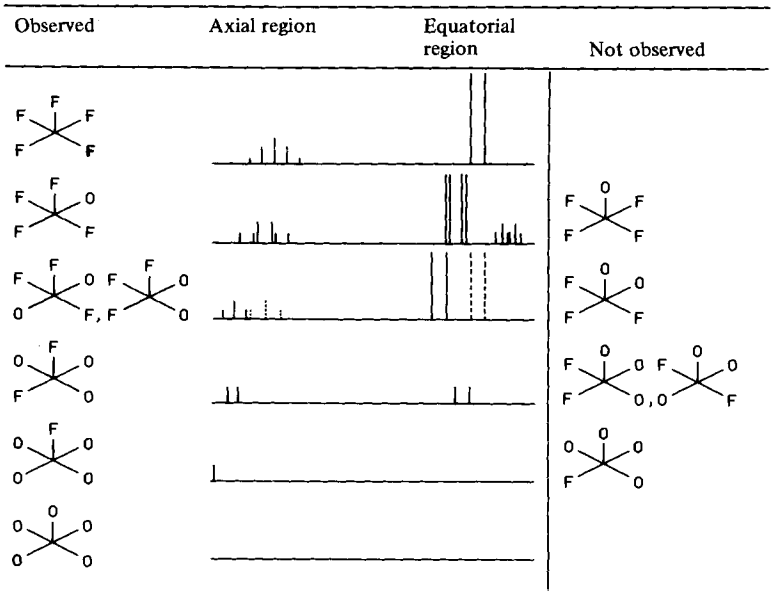


Fig. 1. ^{19}F-NMR spectra of $IF_x(OSeF_5)_{5-x}$ and $IF_x(OTeF_5)_{5-x}$: the signals of F_5SeO and F_5TeO groups (symbolized by O) have been omitted from the schematic representation.

$$IF_5 + B(OTeF_5)_3 \xrightarrow[-BF_3]{20\,^\circ C} FI(OTeF_5)_4 \quad (1)$$

$$FI(OTeF_5)_4 \xrightarrow[-TeF_6]{80\,^\circ C,\ B(OTeF_5)_3} O{=}I(OTeF_5)_3 \quad (2)$$

m. p. 83 °C, subl. 70 °C/10^{-2} mbar

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$$I(OTeF_5)_3 + Xe(OTeF_5)_2 \xrightarrow[-Xe]{20\,^\circ C,\ h\nu} I(OTeF_5)_5 \qquad (3)$$

m. p. 89—94 °C, subl. 65 °C/10^{-2} mbar

The square-pyramidal arrangement of the ligands in $I(OTeF_5)_5$ is confirmed by the appearance of two different ^{19}F-NMR patterns in the intensity ratio 1:4.

$I(OTeF_5)_5$ dissolves in IF_5 to form numerous exchange products belonging to the series $F_xI(OTeF_5)_{5-x}$, whose selenium analogs $F_xI(OSeF_5)_{5-x}$ could be prepared by ligand transfer with $F_2OPOSeF_5$:

$$IF_5 + I(OTeF_5)_5 \rightarrow F_xI(OTeF_5)_{5-x} \qquad (4)$$

$$IF_5 + F_2OPOSeF_5 \xrightarrow[-POF_3]{} F_xI(OSeF_5)_{5-x} \qquad (5)$$

Structural studies on these mixed-substituted compounds by ^{19}F-NMR show that the axial position of the square pyramid is always occupied by a fluorine atom (Fig. 1). Assignment is facilitated by the fact that axial and equatorial fluorine resonance signals occur in different regions and exhibit characteristic coupling constants.

According to the rules of electron pair repulsion (VSEPR theory), the axial position is occupied by the less electronegative ligand, as already found for OCH_3 and C_nF_m[4, 5].

Hence we conclude that the $OSeF_5$ and $OTeF_5$ ligands are more electronegative than fluorine. This also explains why only $FI(OTeF_5)_4$ is formed in reaction (1), because the extremely electronegative ligand will avoid the axial position if possible. Steric effects cannot account for preferential occupation of the equatorial position since crystal structure studies on the very similar compounds *trans*-$F_2Te(OTeF_5)_4$ and $Te(OTeF_5)_6$ rule out mutual hindrance of the $OTeF_5$ groups[1b,c]. Kinetic effects can be discounted since the substitutional behavior is unchanged after several weeks reaction or heating.

In order to better quantify this qualitative observation of extremely high electronegativity, the group electronegativities of the model compounds POF_2—$OTeF_5$, POF_2—$OSeF_5$, POF_3, POF_2Cl, *etc.* were correlated in known manner with the P=O stretching frequencies, ^{31}P-NMR signals, and P—F coupling constants. In all three cases, electronegativities approximately equal to that of fluorine were found for $OSeF_5$ and $OTeF_5$[6].

This abnormal electronegativity can be interpreted by the inductive effect of five fluorine atoms per ligand. Moreover, as shown for the derivatives F_5SOSF_5, $F_5SeOSeF_5$, and $F_5TeOTeF_5$, a pronounced withdrawal of electrons at the oxygen, probably into the d orbitals of the chalcogens, also becomes effective and is especially favored by the contracting action of the five fluorine atoms on these orbitals[1a].

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CAS Registry numbers:
$FI(OTeF_5)_4$, 66270-54-0; $O{=}I(OTeF_5)_3$, 66270-55-1; $I(OTeF_5)_5$, 66270-56-2; $I(OTeF_5)_3$, 49848-13-7; $Xe(OTeF_5)_2$, 25005-56-5; $B(OTeF_5)_3$, 40934-88-1; IF_5, 7783-66-6; $F_2OPOSeF_5$, 63044-18-8

[1] a) *H. Oberhammer, K. Seppelt*, Angew. Chem. *90*, 66 (1978); Angew. Chem. Int. Ed. Engl. *17*, 69 (1978); b) *H. Pritzkow, K. Seppelt*, Inorg. Chem. *16*, 2685 (1977); c) *D. Lentz, H. Pritzkow, K. Seppelt*, Angew. Chem. *89*, 741 (1977); Angew. Chem. Int. Ed. Engl. *16*, 729 (1977).
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Xenon Tetrakis(pentafluoroorthotellurate), $Xe(OTeF_5)_4$[**]

By *Dieter Lentz* and *Konrad Seppelt*[*]

The chemistry of tetravalent xenon has hitherto been limited to XeF_4, which on hydrolysis is converted into the highly unstable compound $XeOF_2$[1]. Since the $OSeF_5$ and $OTeF_5$ groups appear to have an electronegativity resembling that of fluorine[2], it seemed logical to synthesize corresponding derivatives containing these ligands. $Xe(OSeF_5)_2$ and $Xe(OTeF_5)_2$ are already known as the most stable covalent derivatives of XeF_2[3].

We have indeed succeeded in preparing stable $Xe(OTeF_5)_4$—the first compound containing xenon(IV) bound only to oxygen:

$$XeF_4 + B(OTeF_5)_3 \xrightarrow[-BF_3]{0\,^\circ C} Xe(OTeF_5)_4$$

The dark yellow crystalline product melts with decomposition at 72 °C, but can be sublimed *in vacuo* at 50 °C. Its composition and structure were determined by elemental analysis, and by mass [m/e = 859, $Xe(OTeF_5)_3^+$; 618 $Xe(OTeF_5)_2^+$; and other fragments], Raman [127 (90), 145 (88), 230 (60), 241 (81), 297 (3), 309 (19), 320 (7), 335 (9), 418 (100), 649 (27), 662 (91), 709 (40), 721 (24), 750 (16), 782 (11), 827 (3) cm^{-1} (%)]. ^{19}F-NMR [AB_4 spectrum, $\delta_A = 47.2$, $\delta_B = 39.4$, $J_{AB} = 188$ Hz], and ^{129}Xe-NMR spectroscopy [$\delta = 4694$ rel. to Xe, $J_{^{129}Xe\text{-}F} = 61 \pm 1$ Hz, $J_{^{129}Xe\text{-}^{125}F} = 1005 \pm 15$ Hz].

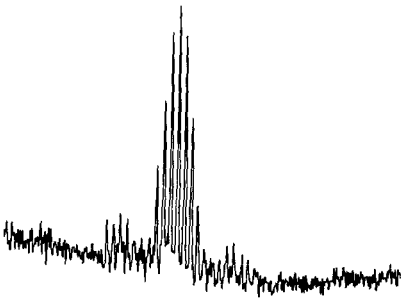


Fig. 1. ^{129}Xe-NMR spectrum of $Xe(OTeF_5)_4$, solution in perfluorobutanesulfonyl fluoride.

Tetravalency is confirmed above all by the ^{129}Xe-NMR spectrum (Fig. 1). The chemical shift closely resembles that in XeF_4[4a], whereas compounds of divalent xenon have signals in other characteristic regions[4]. Coupling with the tellurium isotope ^{125}Te and the 16 equatorial fluorine atoms proves the existence of the compound.

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The driving force of decomposition according to

$$Xe(OTeF_5)_4 \xrightarrow{72\,^\circ C} Xe(OTeF_5)_2 + F_5TeO{-}OTeF_5$$

$$XeF_4 \xrightarrow{ca.\ 450\,^\circ C} XeF_2 + F_2$$

is the strong peroxide bond in $F_5TeOOTeF_5$[5]; in contrast, the analogous decomposition of XeF_4 occurs at much higher temperatures owing to the weak bond present in molecular fluorine[6].

The analogous selenium compound $Xe(OSeF_5)_4$ has not yet been prepared because the required ligand transfer agent $B(OSeF_5)_3$ is not yet available.

Procedure

XeF_4 (1.5 g, 7.2 mmol) is transferred into a quartz trap under argon. To this compound is condensed perfluoro-*n*-hexane (10 ml) and $B(OTeF_5)_3$ (8.8 g, 12.1 mmol) in a dynamic vacuum. The mixture is warmed to $-78\,^\circ C$; evolution of gaseous BF_3 increases as the mixture is warmed to room temperature. All volatile components are subsequently removed at room temperature in an oil-pump vacuum. The residue is $Xe(OTeF_5)_4$, yield 7.2 g (92%).

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$Xe(OTeF_5)_4$, 66255-64-9; XeF_4, 13709-61-0; $B(OTeF_5)_3$, 40934-88-1

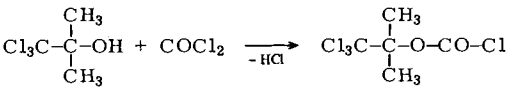
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The 2,2,2-Trichloro-*tert*-butyloxycarbonyl Group (TCBOC)—An Acid- and Base-Resistant Protecting Group Removable under Mild Conditions[**]

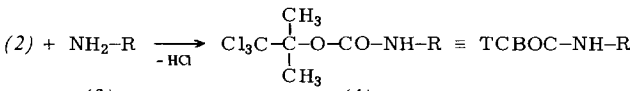
By *Heiner Eckert, Monika Listl*, and *Ivar Ugi*[*]

β-Haloalkoxycarbonyl protecting groups[1-6] are important because they can be removed selectively. The protecting groups 2-chloro-[2], 2-bromo-[3,4], 2-iodo-[4], and 2,2,2-trichloroethoxycarbonyl[5], and also 2-bromo-*tert*-butyloxycarbonyl[6] all show some degree of base lability which limits their preparative scope. However, we have discovered that the 2,2,2-trichloro-*tert*-butyloxycarbonyl group (TCBOC) is so stable towards acids and bases that conditions are fulfilled for its wide application.

The TCBOC group can be introduced by means of the stable and distillable chloroformate *(2)*, which is readily accessible from 2,2,2-trichloro-*tert*-butanol (chloretone) *(1)* and phosgene in dichloromethane or pyridine. Chloretone itself is an inexpensive commercially available reagent.



(1) *(2)*



(3) *(4)*

NH_2–R = amino acid or peptide ester

Table 1. Yields of TCBOC-protected components in the synthesis of tetrapeptide *(4f)*.

Reaction		Yield [%]
(3a) → *(4a)*	TCBOC-Val-OH	82
(4a) → *(4b)*	TCBOC-Val-Ala-OMe	90
(4b) → *(4c)*	TCBOC-Val-Ala-OH	82
(4c) → *(4d)*	TCBOC-Val-Ala-Phe-O*t*Bu	67
(4d) → *(4e)*	TCBOC-Val-Ala-Phe-OH	82
(4e) → *(4f)*	TCBOC-Val-Ala-Phe-Phe-O*t*Bu	94

Reaction of *(2)* with the amino acids or peptide esters *(3)* can be accomplished under the usual Schotten-Baumann conditions. Thus, on treatment with *(2)*, valine *(3a)* affords the TCBOC-protected amino acid *(4a)* in good yield (see Table 1). Subsequent synthesis of the tetrapeptide *(4f)* by the DCCD/HO-Su method[1] proceeds without difficulty (apart from the problems of separation encountered in product work-up after linkage by this method); the excellent crystallization properties of the TCBOC-protected products warrant particular mention. The pronounced hydrophobic behavior of the TCBOC group endows the compounds *(4)* with good solubility in organic solvents such as dichloromethane. The group is easily recognized in the ^{1}H-NMR spectrum by virtue of a characteristic singlet at $\delta = 2.0$.

Table 2. Stability of the N-terminal TCBOC group towards acidic and basic reagents.

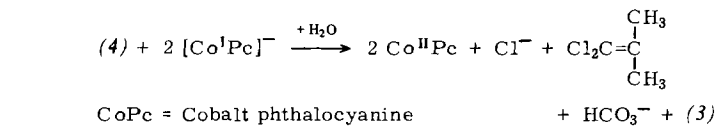
		Conditions	Stability of the C-terminal group	Stability of the TCBOC group
(4g)	TCBOC-Val-OMe	0.1 N NaOH/20 °C/2 h	+	+
(4g)	TCBOC-Val-OMe	1 N NaOH/40 °C/2 h	−	(+) [a]
(4b)	TCBOC-Val-Ala-OMe	0.1 N NaOH/20 °C/2 h	−	+
(4g)	TCBOC-Val-OMe	TFA [b]/20 °C/2 h	+	+
(4d)	TCBOC-Val-Ala-Phe-O*t*Bu	TFA [b]/20 °C/1 h	−	+

[a] 40% of TCBOC-Val-OH are formed.
[b] TFA = trifluoroacetic acid.

The TCBOC group proves to be inert on alkaline hydrolysis of the methyl ester *(4b)* to give *(4c)*, and on acidic cleavage of the *tert*-butyl ester *(4d)* to give *(4e)* (see Table 2).

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CoPc = Cobalt phthalocyanine

Removal of the TCBOC group can be accomplished with the supernucleophilic cobalt(I)-phthalocyanine anion in methanol or acetonitrile[3, 7, 8] and with zinc in glacial acetic acid (see Table 3); the yields of amine component are 66—94%. N-Terminal deprotection by lithium cobalt(I)-phthalocyanine also proceeds smoothly in the case of benzyl esters.

Table 3. Removal of the TCBOC group from compounds *(4)* by lithium cobalt(I)-phthalocyanine in methanol (method A) or acetonitrile (method B) or with zinc in glacial acetic acid (method C) at 20 °C.

	(4)	Method	Reaction time	Yield of *(3)* [%]
(4g)	TCBOC-Val-OMe	A	1 min	87
(4h)	TCBOC-Val-OCH_2Ph	A	1 min	93
(4d)	TCBOC-Val-Ala-Phe-O*t*Bu	B	1 h [a]	94
(4g)	TCBOC-Val-OMe	C	3 h	66
(4d)	TCBOC-Val-Ala-Phe-O*t*Bu	C	3 h	73

[a] The actual deprotection reaction only takes 5 min.

Experimental

Synthesis of *(2)*: Anhydrous chloretone *(1)* (178 g, 1.0 mol) dissolved in anhydrous dichloromethane (400 ml) is treated at −20 °C with phosgene (140 ml, 2.0 mol). Pyridine (105 ml, 1.5 mol) in dichloromethane (70 ml) is added dropwise at −20 °C and the mixture is then stirred for 12 h at 20 °C. Subsequent washing of the ether solution at 0 °C with water (caution: vigorous evolution of gas owing to liberation of excess phosgene), 2 N sulfuric acid, and water followed by distillation affords 214 g (89%) of *(2)*, b. p. 77—81 °C/12 torr.

Synthesis of *(4a)*: Valine (11.7 g, 0.1 mol), dissolved in water (200 ml) and 1 N sodium hydroxide solution (250 ml), is treated with diethyl ether (100 ml) and then emulsified at 0 °C with *(2)* (33.8 g, 0.14 mol) in dioxane (140 ml) for 1 h. The aqueous phase is washed with diethyl ether, acidified with 5 N hydrochloric acid, and extracted into ethyl acetate. After washing with water, compound *(4a)* (26 g, 82%) crystallizes from the extract; the product is recrystallized from hexane; m. p. 102 °C.

Deprotection of *(4d)* (method B): A solution of lithium cobalt(I)-phthalocyanine[3, 7, 8] (2.5 g, 2.8 mmol) in acetonitrile (15 ml), phenol (600 mg, 6 mmol), and *(4d)* (500 mg, 0.84 mmol) are stirred together at 20 °C under N_2 for 1 h. Water (20 ml) and 1 N HCl (2 ml) are added to the dark green mixture; the dark blue precipitate is centrifuged off, and the residue is washed with 1% citric acid and water. The supernatant liquors (pH 4.0) are washed with ether, rendered alkaline with Na_2CO_3 and extracted with ethyl acetate. Evaporation of the extract affords *(3d)* (310 mg, 94%) (identification by ^{1}H-NMR, IR).

Deprotection of *(4d)* (method C): Compound *(4d)* (595 mg, 1.0 mmol) is dissolved in 95% acetic acid (10 ml) and zinc dust (*ca.* 1 g) is added portionwise over 3 h to the stirred solution. Zinc is then filtered off, washed with water, and the filtrate and washings washed with ether. After rendering alkaline with caustic soda solution and extraction with ethyl acetate, *(3d)* (286 mg, 73%) is obtained from the extract by evaporation (identification by ^{1}H-NMR, IR).

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(2), 66270-36-8; *(3a)*, 72-18-4; *(3d)*, 66270-37-9; *(4a)*, 66270-38-0; *(4b)*, 66270-39-1; *(4c)*, 66270-40-4; *(4d)*, 66270-41-5; *(4e)*, 66270-42-6; *(4f)*, 66270-43-7; *(4g)*, 66270-44-8; *(4h)*, 66270-45-9

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Preparation and Some Reactions of Dimethyl(trimethylsilylimino)silane, $Me_2Si{=}NSiMe_3$[1]

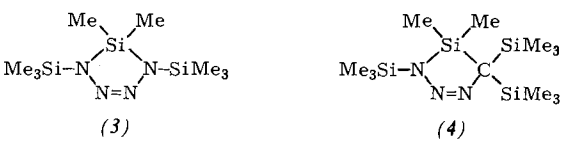
By *Nils Wiberg* and *Gerhard Preiner*[*]

Having synthesized the silaethene *(1)*[2], we have now found a facile entry to iminosilane *(2)*—a representative of the poorly characterized, highly reactive compounds containing a Si=N double bond which have not yet been isolated[3].



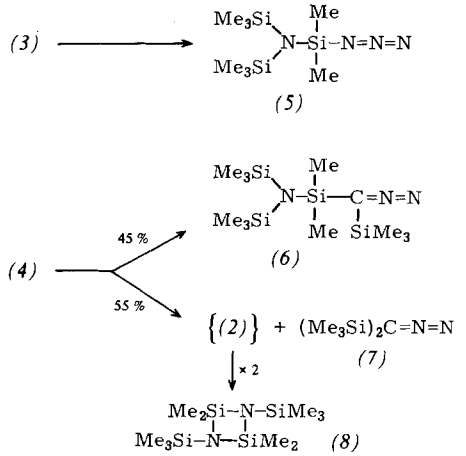
(1) *(2)*

Our study was prompted by observation of differing behavior on thermolysis of the "isosteric" heterocycles *(3)* and *(4)*:



(3) *(4)*

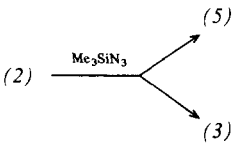
While thermolysis of *(3)* at 180 °C leads quantitatively *via* isomerization to the aminosilyl azide *(5)*[4], compound *(4)* (readily accessible from *(1)* and Me_3SiN_3; metastable below −5 °C)[2, 5] is not converted exclusively into *(6)* (analogous to *(5)*); fragmentation also occurs, affording the iminosilane *(2)*, which dimerizes to *(8)* in the absence of a trapping reagent, and the diazomethane derivative *(7)*[5].



(5) *(6)* *(7)* *(8)*

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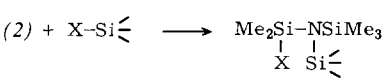
Evidence for the intermediacy of *(2)* is provided (i) by the insensitivity of the yields of *(6)* and *(7)* to addition of a trapping agent for *(2)*[6], and (ii) by the fact that the product yields according to



are independent of the source of *(2)*[7].

Like *(1)*[2], *(2)* shows an, albeit considerably lower, tendency to undergo *cycloaddition* to multiple bond systems. Thus *(2)* reacts with itself or with benzophenone in a [2+2] cycloaddition. Unlike *(1)*, however, *(2)* does not react with bis(trimethyl)diazene to form four-membered rings. Moreover, [2+3] cycloaddition of *(2)* and trimethylsilyl azide to give *(3)* plays only a minor role, especially at low temperatures (0°C)[8], whereas *(1)* reacts quantitatively with Me_3SiN_3 to form *(4)*. Dienes which can form Diels-Alder adducts with *(1)* could not formerly be subjected to [2+4] cycloaddition with *(2)*.

On the other hand, the tendency to undergo *insertion* into single bonds of type $\geqslant$Si—X according to



appears to be greater for *(2)* than for *(1)*. Thus *(2)* and trimethylsilyl azide give *(5)* in high yields, whereas the silaethene *(1)* does not insert at all into the Si—N bond of Me_3SiN_3. Trimethylsilyl chloride also reacts with *(2)* mainly according to the above equation (slight dimerization of *(2)* occurs), but only to a limited extent with *(1)*. Hexamethylcyclotrisiloxane still gives an eight-membered ring with *(2)* (dimerization of *(2)* is the principal reaction), but not with *(1)*[9].

Procedure

BuLi (0.79 mmol) in diethyl ether (2 ml), and then Me_3SiN_3 (91 mg, 0.79 mmol) in diethyl ether (1 ml) are added dropwise to $TosOSiMe_2$—$CBr(SiMe_3)_2$[2] (370 mg, 0.79 mmol) dissolved in a mixture of diethyl ether (5 ml) and tetrahydrofuran (5 ml) cooled to −110°C. The reaction mixture is first warmed to −55°C, whereupon *(4)* and insoluble TosOLi are formed, and then—after addition of the desired reactant for *(2)*—to room temperature.

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(1), 62139-73-5; *(2)*, 66239-89-2; *(3)*, 66239-88-1; *(4)*, 66239-87-0; *(5)*, 66239-86-9; *(6)*, 66239-85-8; *(7)*, 30006-66-7; *(8)*, 2954-84-9; $TosOSiMe_2$—$CBr(SiMe_3)_2$, 62182-97-2; Me_3SiN_3, 4648-54-8

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[4] *N. Wiberg, G. Ziegleder*, Chem. Ber. *111*, No. 6 (1978).
[5] Corresponding heterocycles metastable up to about 35°C are obtained from *(1)* and organyl azides (*e.g.* R=Ph, tolyl); they decompose by isomerization and fragmentation like *(4)*.
[6] The trapping agent does not react directly with *(4)*.
[7] According to our findings, *(2)* is also formed by thermolysis (*ca.* 90°C) of the [2+2] cycloadduct [2] accessible from *(1)* and $Me_3SiN{=}NSiMe_3$.
[8] At higher temperature (90°C), *(3)* is formed in about 20% yield alongside *(5)*.
[9] *Note added in proof* (April 15, 1978): The efficacy of compounds $\geqslant$SiX as trapping agents for *(2)* increases along the series $(Me_2SiO)_3 \ll Me_3SiNMe_2 < Me_3SiOMe < Me_3SiCl < Me_3SiN_3$.

Chiral Polysiloxanes for Resolution of Optical Antipodes[**]

By *Hartmut Frank, Graeme, J. Nicholson*, and *Ernst Bayer*[*]

Enzymes and receptors are responsible for the specific reactions and recognition of optical antipodes in nature. In the case of synthetic drugs too, one enantiomer is usually more active than the other. Proteins can thus undergo selective interaction with enantiomers from an enormous variety of substances. We have attempted to impart nature's enantiomeric selectivity to synthetic polymers with amino acid groups.

In order to study such interactions between optically active substrate and an amino acid or peptide group as active site, we have synthesized polymeric organosiloxanes to which an active site, *e.g.* an L-amino acid, is linked with dicyclohexylcarbodiimide in the final synthetic step. Introduction of this site at an earlier stage proved unsatisfactory owing to the danger of racemization. Suitable polymeric backbones are copolymers of poly[(2-carboxylpropyl)methylsiloxane], octamethylcyclotetrasiloxane, and hexamethyldisiloxane; an amino acid or peptide group is linked as amide to the terminal carboxylic group.

The individual chiral centers must be separated by a siloxane chain of certain length to achieve optimum interaction and viscosity of the polymer.

The polymer-substrate interaction has been studied by gas chromatography. There is still no stationary phase of wide applicability for the gas chromatographic resolution of enantiomers. Not all enantiomeric pairs of natural amino acids can be separated with the low-molecular phases developed for amino acids by *Gil-Av*[1].

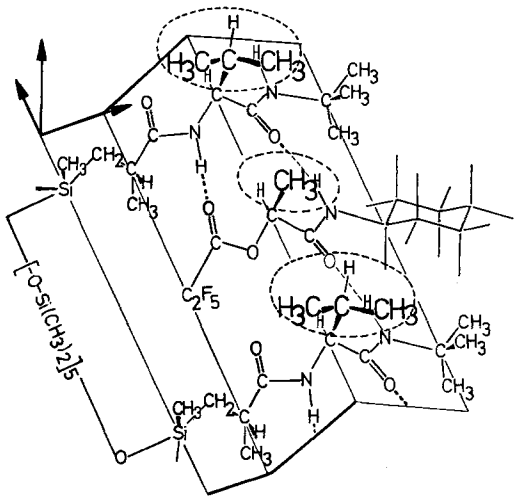
The new polysiloxanes with covalently bound amino acid or peptide groups can be used as stationary phases between 70 and 240°C. They effect direct separation of optical antipodes from widely diverse classes of compounds such as amino acids[2], hydroxy acids, alcohols, amines, and biphenyl derivatives without any need for preparation of diastereomers.

D- or L-Amino acids or their peptides can be bound as chiral centers to the organosiloxane. *N-tert*-Butyl-L-valinamide joined to the carboxyl group of the copolymeric organosiloxane by a peptide linkage has proved of great value for optical resolutions (Scheme 1).

Glass capillaries are coated by known methods[4] with this phase, which we designate Chirasil-Val[3], containing 0.86 mmol L-amino acid/g of polymer. The compounds are converted into the volatile *N,O*-bis(pentafluoropropionyl) derivatives[5] prior to gas chromatography, which is then performed under the conditions given in Figure 1. In all the cases examined so far, the D enantiomer is eluted from an L-amino acid phase before the L form.

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Scheme 1

The structure of the diastereomeric association complex is illustrated for *N*-cyclohexyl-*O*-pentafluoropropionyl-L-lactamide which elutes after the D enantiomer and whose association complex with Chirasil-L-Val is more stable than the complex with the D enantiomer. As in the pleated sheet structure of β-keratin, this conformation (Scheme 1) permits formation of the maximum number of hydrogen bonds. The space-filling isopropyl and methyl groups on the asymmetric carbon atom of the "receptor" and the "substrate", respectively, and the C-terminal alkylamide groups fit together as stacked layers and stabilize the structure by van der Waals forces. No such stacking is possible when the substrate has the D configuration; mutual hindrance of the isopropyl and methyl groups leads to a less stable association complex and earlier elution. The significance of the dimethylsiloxane units is also apparent from a model; they keep the L-valinamide units at a distance and prevent formation of intramolecular hydrogen bonds which would give the polymer a quasicrystalline structure.

Chirasil-Val has been used for determining the racemization of natural amino acids, for purity checks on glycols and biphenyl derivatives, and for separation of enantiomeric biogenic amines and hydroxy acids. The separation factors for optical antipodes expectedly increase with decreasing separation temperature. Figure 1 shows a chromatogram of some substances used as drugs whose enantiomeric composition can now be established conveniently and rapidly.

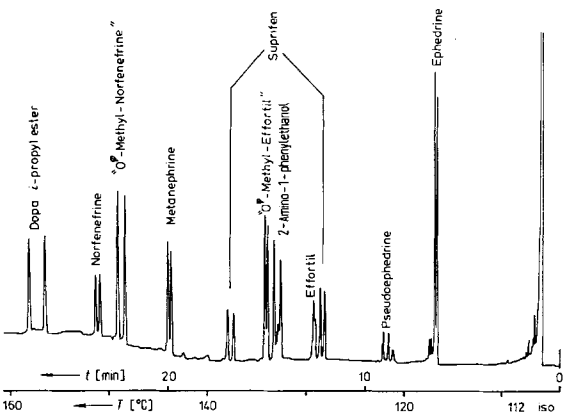
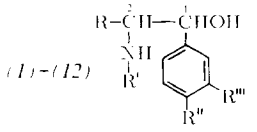


Fig. 1. Gas chromatographic separation of the enantiomeric pairs of drugs and metabolites as *N,O*-per(pentafluoropropionyl) derivatives on Chirasil-Val. 20 m × 0.3 mm glass capillary, hydrogen at 0.3 bar as carrier gas, temperature of injection block and detector 250 °C.

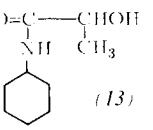
Apart from practical analytical aspects, considerable importance attaches to studies on interaction as a function of structure. Table 1 lists the separation factors of the enantiomers of some 2-amino-1-phenylethanols which occur naturally and are used as drugs. The following substituent effects are observed:

a) Separation factors are small for alkylated amino groups (R′ = alkyl). Since there is no hydrogen atom left for hydrogen bonding after derivatization, "three-point attachment"[6] is impossible and the diastereomeric association complex is less stable [norephedrine *erythro-(12)* → ephedrine *erythro-(3)*; norfenefrine *(9)* → etilefrine *(1)*].

b) Replacement of a hydrogen atom at C-2 by a methyl group (R = CH_3) increases the difference in stability of the diastereomeric complexes. In the case of the "parallel"



(1)–(12)



(13)

Table 1. Separation factors for *N,O*-per(pentafluoropropionyl) derivatives of the antipodes of compounds *(1)*—*(13)* on a 20 m × 0.3 mm glass capillary column charged with Chirasil-Val.

Cpd.	R	R′	R″	R‴	Name	Separation factor $\alpha_{L/D}$ at 110 °C	at 160 °C
(1)	H	C_2H_5	H	OH	Etilefrine (effortil)	1.014	
(2)	H	C_2H_5	H	OCH_3	"O^{Φ}-Methyl-effortil"	1.024	
(3) erythro	CH_3	CH_3	H	H	Ephedrine	1.028	
(4)	H	CH_3	OH	OCH_3	Metanephrine	1.031	
(5) erythro	CH_3	CH_3	OH	H	*p*-Hydroxyephedrine (suprifen)	1.040	
(3) threo	CH_3	CH_3	H	H	Pseudoephedrine	1.050	
(5) threo	CH_3	CH_3	OH	H	*p*-Hydroxyephedrine (suprifen)	1.053	
(6)	H	H	H	H	2-Amino-1-phenylethanol	1.059	1.038
(7)	H	CH_3	OH	H	Synephrine		1.014
(8)	H	H	OH	OH	Norepinephrine		1.018
(9)	H	H	H	OH	Norfenefrine		1.027
(10)	H	H	OCH_3	OCH_3	2-Amino-1-(3,4-dimethoxyphenyl)ethanol		1.032
(11)	H	H	H	OCH_3	"O^{Φ}-Methyl-norfenefrine"		1.042
(12) erythro	CH_3	H	H	H	Norephedrine		1.058
(13)		[a]			*N*-Cyclohexyllactamide	1.102	

[a] Examined as the *O*-pentafluorpropionyl derivative.

complex, the methyl group is directed away from the isopropyl side chains of the valine groups; in the diastereomeric complex they hinder each other to such a degree that optimum approach of the *N*-proton of the substrate and the carbonyl group of valine is impossible [*(6)* → norephedrine *erythro-(12)*; synephrine *(7)* → *p*-hydroxyephedrine *(5)*].

c) The influence of substitution in the phenyl ring is less clear-cut. A *m*-hydroxyl group has a deleterious effect upon the separation of the two antipodes. A *p*-hydroxyl group favors a stereospecific association of the secondary amines [ephedrine *erythro-(3)* → *p*-hydroxyephedrine *(5)*; *(2)* → metanephrine *(4)*], but is unfavorable with primary amines. In the former case, "two-point attachment" is probably stabilized by participation of the carbonyl of the *O*-acyl group to give a "third point"; in primary amines this would lead to competition between two association conformations.

Analogies become apparent on comparison of the observed effects with biological activities. As in gas-chromatographic systems, the differences in the sympathomimetic effect between the D and the L form are greater when C-2 bears an additional methyl group ($R = CH_3$). While the difference in the dose/action curve consists merely in a shift of the concentration for the enantiomers of norepinephrine, an additional lowering of the maximum efficacy of the L enantiomer compared to that of the D enantiomer is observed with the corresponding 2-methyl compound cobefrin (and all other 2-methyl compounds)[7]. As in gas chromatography, where interaction of the amino acid residues with secondary amines is lower, these compounds also exhibit lower activities than primary amines in some biological systems[8].

The use of such polymeric stationary phases facilitates investigation of the interaction between two optically active molecules over a wide range of temperature. We are now one step closer to the synthesis of "tailored" chiral matrices, and the requirements for the stereospecificity of catalyst systems can be better examined. At the same time, these organosiloxanes represent yet another example of the imitation of the properties of biopolymers by synthetic polymers[9].

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Stable L-(+)-Ascorbic Acid Radical Anions

By *Hartmut B. Stegmann, Klaus Scheffler*, and *Paul Schuler*[*]

The great biochemical significance of L-(+)-ascorbic acid has induced numerous authors to undertake ESR studies on the radicals formed on oxidation[1]. The reactivity of the radicals requires their generation by methods permitting maintenance of an adequate steady concentration of paramagnetic particles in the ESR cavity. However, side reactions also occurred and mixed spectra were observed.

On studying paramagnetic ion pairs with organometal cations[2] we found that the half-lives of paramagnetic anions can be considerably extended by complexation. We have therefore examined the oxidation of L-(+)-ascorbic acid in the presence of diarylthallium hydroxides.

Immediately after mixing, equimolar mixtures of R_2TlOH and ascorbic acid in pyridine as solvent show distinct ESR signals which reach maximum intensity after *ca.* 3 h. The concentration of the radicals formed by autoxidation can be greatly increased by addition of lead dioxide without giving rise to any further changes in the ESR spectra. The hyperfine structure (cf. Fig. 1) comprises four triplets, corresponding to coupling with two protons which are equivalent within the linewidth, with a single proton, and with the magnetic thallium nuclei.

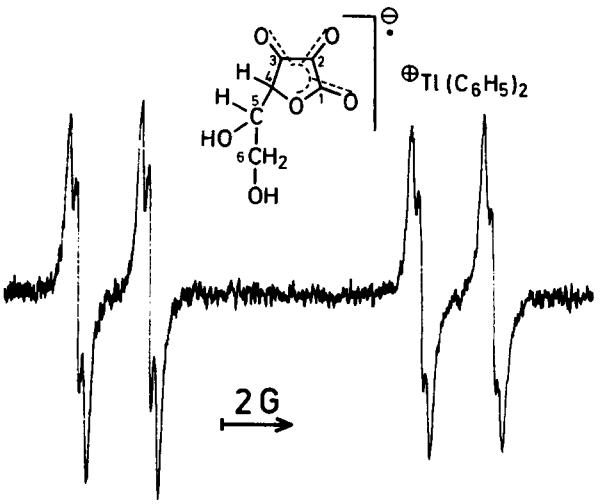


Fig. 1. ESR spectrum of the L-(+)-ascorbic acid radical anion-diphenylthallium complex in pyridine at room temperature.

We assigned the proton coupling constants (Table 1) by analogy with earlier studies[11]. The fact that the greatest coupling constant is due to the thallium nuclei follows (i) from the unusually large temperature dependence and (ii) from the pronounced substituent effect (Table 1).

Table 1. ESR data of paramagnetic ascorbic acid-diarylthallium complexes.

	$R_2Tl^{\oplus}$ R=	$a_{C_6}^{H_2}$ [G]	$a_{C_4}^{H_1}$ [G]	a_{Tl} [G]	g	ΔH [G]
(1)	C_6H_5	0.245	2.10	9.95	2.0051	0.15
(2)	$C_6H_3Me_2$-2,5	0.250	2.06	5.19	—	0.13
(3)	$C_6H_2Me_3$-2,4,6	0.270	2.4	6.5	2.0050	0.2
(4)	C_6F_5	—	2.0	61.75	—	1.0

The complexed radical anions are very stable. Thus, the half-life of *(1)* is of the order of days. In order to establish whether there is a quantitative relation between ascorbic acid concentration and peak-to-peak signal intensities, we have conducted preliminary studies on *(1)* at a modulation amplitude of 800 mG and a microwave output of 2 mW. Under these conditions a linear dependence of the signal intensity upon the concentration was detected, provided that comparable oxidation conditions were used. The experimental values were reproducible within 10%. This precision and the sensitiv-

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ity of detection can be enhanced considerably, particularly by cation variation, thus permitting quantitative determination of L-(+)-ascorbic acid.

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[1] For a review, see *G. P. Laroff, R. W. Fessenden, R. H. Schuler*, J. Am. Chem. Soc. *94*, 9062 (1972).
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Mineralization of Chlorofluorocarbons in the Sunlight of the Troposphere

By *Siegmar Gäb, Johannes Schmitzer, Hans-Willi Thamm*, and *Friedhelm Korte*[*]

Rowland and *Molina*'s hypothesis[1] that chlorofluorocarbons (CFC's) destroy the ozone layer of the atmosphere is the topic of lively discussion[2]. One of the premises of this hypothesis, the infinite tropospheric lifetime of CFC's, has been questioned on the basis of recent experimental findings. Thus studies performed by *Ausloos et al.* showed that irradiation of perhalogenated CFC's with long wavelength UV light ($\lambda > 300$ nm) in the presence of quartz sand and C_2H_6 gives chlorinated ethanes (major product: C_2H_5Cl)[3]. Our own work on the oxidative degradation of persistent chlorohydrocarbons by heterogeneous photolysis[4] suggested that FHC's are also decomposed under these conditions.

For our investigations we chose silica gel (Kieselgel 60, Merck) as adsorbent since the silicon dioxide surface can be regarded as representative of many natural dusts and sands[5], permitting a qualitative analogy with atmospheric conditions. Measurements of the adsorption of CCl_2F_2 on various samples of natural Sahara sand (Libya Desert Soil, Algadones Dune Sand) and synthetic materials (Aerosil 200, Kieselgel 60) reveal only a slight influence of chemical composition of the sample upon the surface coverage. The adsorption isotherm measured for Kieselgel 60 corresponds to the average value from the isotherms of the two natural dusts[6].

We were able to detect formation of mineralization products (CO_2, CO, and HCl) both on irradiation of the CFC's (CCl_2F_2 and CCl_3F) adsorbed on silica gel with UV light from a high-pressure Hg lamp and on exposure of the sample to natural sunlight at ground level. The decomposition rates listed in Table 1 show a significant dependence upon the wavelength range of the incident UV light. In contrast to irradiation through Pyrex glass (P), irradiation through quartz glass (Q) resulted in the formation of Cl_2 and enhancement of the decomposition rate, possibly by a homogeneous photolysis running in parallel[7].

Even on considering the values measured in sunlight (S), the magnitude of the effect in the troposphere can only be roughly estimated so that any conclusions regarding tropospheric lifetimes are surrounded by some uncertainty. This is due mainly to the inhomogeneous energetic nature of the surface of the adsorbent, which leads to a rise in adsorption energy with decreasing partial pressure of CFC's[6]. A possible related effect on the decomposition rate of CFC's has yet to be studied in detail. Thus at the present stage we consider predictions of the decomposition rate under tropospheric conditions to be premature owing to the need to extrapolate over several orders of magnitude (partial pressure of $CFC_{reactor}$: partial pressure of $CFC_{troposphere} \approx 10^8$). Comparison with other classes of compounds serves for preliminary evaluation. Thus it could be shown that the photooxidative decomposition of CFC in the above simulation model clearly lies below that of chlorinated C_2, C_3 olefins (easily degradable) and is comparable with that of several methyl- and chlorine-substituted benzenes (poorly degradable)[4d].

Table 1. Photochemical decomposition of CCl_2F_2 and CCl_3F, adsorbed on silica gel [a].

		Mineralization products [%] [e]			
		CO_2	CO	Cl_2	HCl
CCl_2F_2	(Q) [b]	18.0	<1.0	10.6	3.2
	(P) [c]	1.4	<1.0	—	0.8
	(S) [d]	9.1	+	–	5.7
CCl_3F	(Q)	67.6	<1.0	35.2	2.8
	(P)	4.1	<1.0	–	2.2
	(S)	23.4	+	–	9.4

[a] Gaseous CFC (8 mmol) was passed into the evacuated reactor containing Kieselgel 60 (Merck) (200 g) with continuous mixing of adsorbent and gas phase. Oxygen was then passed in until atmospheric pressure was reached.
[b, c] Irradiation with a Hg high pressure lamp (HPK 125 W, Philips): [b] 48 h through quartz glass; [c] 144 h through Pyrex glass.
[d] Exposure to natural sunlight was performed for 170 h between September 7 and 28, 1977 (54 h overcast, 31 h cloudy, 85 h almost cloudless).
[e] The percentages were calculated from the ratios of the experimental amounts to the theoretically possible amounts; +, product formation; –, no product formation.

Experimental

UV irradiation was performed in a sealed rotating reactor drum with constant mixing of carrier with the adsobed phase and the gas phase[4b]. While the light source for the laboratory experiments was located in a half-closed Pyrex or quartz glass tube which projected into the reactor along its rotation axis, exposure to natural sunlight was through the wall of a quartz reactor. After irradiation, the reactor was flushed for *ca.* 12 h with O_2 and the gas stream first passed through 0.1 N NaOH to absorb CO_2 and Cl_2. The CO was trapped as CO_2 in NaOH after catalytic oxidation of the gas stream[8]. HCl was obtained by stirring the silica gel with aqueous NaOH. Quantitative determination of the mineralization products was performed by acidometric (CO and CO_2), iodometric (Cl_2), and potentiometric titration (HCl).

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German version: Angew. Chem. 90, 398 (1978)

CAS Registry numbers:
CCl_2F_2, 75-71-8; CCl_3F, 75-69-4

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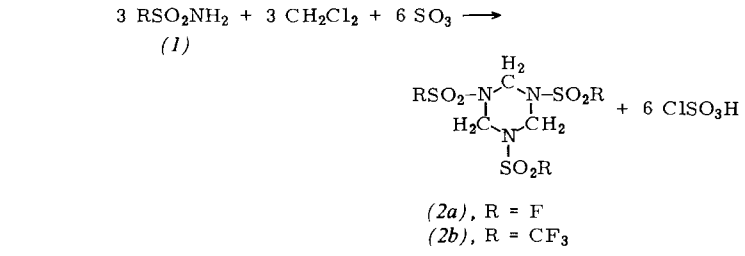
[1] *M. J. Molina, F. S. Rowland*, Nature (London) *249*, 810 (1974).
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[5] *A. W. Castleman, Jr.*, University of Colorado, Boulder, Col., personal communication.
[6] *W. Roth*, Hoechst AG, Frankfurt, personal communication.
[7] *C. Hubrich, C. Zetzsch, F. Stuhl*, Ber. Bunsenges. Phys. Chem. *81*, 437 (1977).
[8] Catalyst: COEX 0.3 (Dr. E. Dürrwächter DODUCO KG, D-6920 Sinsheim), 150°C.

Methylene Chloride as a Reagent for Cyclizations with SO_3 as HCl Trapping Agent[**]

By *Herbert W. Roesky, Minoru Aramaki*, and *Lothar Schönfelder*[*]

Owing to its inertness, methylene chloride is usually employed as solvent and not as reactant. To our knowledge methylene chloride has hitherto not been observed to react with amides or amines at room temperature with concomitant loss of hydrogen chloride. We have now found that such reactions can indeed readily take place in the presence of sulfur trioxide as HCl trapping reagent. When fluorosulfonamide *(1a)* or trifluoromethane sulfonamide *(1b)* is allowed to react with "SO_3 in CH_2Cl_2" the corresponding 1,3,5-tris(sulfonyl)-1,3,5-triazacyclohexane *(2)* and chlorosulfonic acid are formed.



(2a), R = F
(2b), R = CF_3

The products *(2a)* and *(2b)* are crystalline white products, m.p. 217 and 211°C, respectively. The six-membered ring structure of the molecules manifests itself in the spectroscopic data: The mass spectrum of *(2a)* shows the molecular ion at $m/e = 333$ (3%) along with fragments at 222 $(FSO_2NCH_2)_2$ 20%, 111 FSO_2NCH_2 20%, 113 FSO_2NHCH_3 100%. ^{19}F-NMR: $\delta = -54.8$, quintet; ^{1}H-NMR: $\delta = 5.5$, quartet, $J_{HF} = 1.5$ Hz. The mass spectrum of *(2b)* likewise shows a trimer at $m/e = 483$ with a relative intensity of 2%. The ^{19}F-NMR spectrum shows only one signal, $\delta = 77.6$ (rel. $CFCl_3$ ext.)[1].

Experimental

SO_3 (0.3 mol) is added dropwise to a suspension of *(1)* (0.1 mol) in methylene chloride (0.25 mol). A weakly exothermic reaction takes place with formation of a white precipitate. After 24 hours' stirring, excess CH_2Cl_2 and SO_3 are removed by evaporation in a vacuum and the solid product isolated by filtration. *(2a)* can be purified by recrystallization from a mixture of CH_3CN and CCl_4, *(2b)* from CH_3CN; yields: 75% and 42% respectively.

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

CAS Registry numbers:
(1a), 14986-54-0; *(1b)*, 421-85-2; *(2a)*, 30277-57-7; *(2b)*, 66183-94-6; methylene chloride, 75-09-2

[1] *H. W. Roesky, M. Diehl, H. Fuess, J. W. Bats*, Angew. Chem. *90*, 73 (1978); Angew. Chem. Int. Ed. Engl. *17*, 58 (1978); *H. W. Roesky, M. Aramaki, ibid. 90*, 127 (1978) and *17*, 129 (1978), respectively.

Contamination of Amines with *N*-Nitrosamines[**]

By *Bertold Spiegelhalder, Gerhard Eisenbrand*, and *Rudolf Preussmann*[*]

During studies on trace analysis of carcinogenic nitrosamines in the environment[1], we have discovered that commercially available secondary and tertiary amines are contaminated with the corresponding nitrosamines. Concentrations in samples from various manufacturers varied between 0.03 and 53.0 mg/kg. The results of 35 determinations are shown in Table 1. Only in exceptional cases were other nitrosamines present; presumably, their occurrence is due to contamination with other amines.

Table 1. Contamination of secondary and tertiary amines with the corresponding dialkyl-*N*-nitrosamine.

Amine investigated	Concentration [mg/kg]	$\bar{X}$ [a]	n [b]
Dimethylamine solution	0.65—17.3	6.72	6
Dimethylamine hydrochloride	0.21		1
Diethylamine	0.1—7.3	1.78	6
Dipropylamine	1.9—13.0		2
Diisopropylamine	0.25—0.39		2
Dibutylamine	0.3—2.95	1.34	6
Diisobutylamine	8.35		1
Dipentylamine	0.31—2.6	1.4	3
Dihexylamine	0.4		1
Piperidine	1.6—2.1		2
Pyrrolidine	3.65—53.0	25.65	4
Triethylamine	0.03 [c]		1

[a] $\bar{X}$ = average value from several samples. [b] n = number of samples from different sources. [c] Diethylnitrosamine.

For analysis, a sample of the amine (0.5—1 g) is steam distilled at reduced pressure. After acidification with 2N H_2SO_4, the distillate is extracted with dichloromethane. Nitrosamine could be separated from the concentrated extract by gas chromatography (5 m steel column, $\frac{1}{8}$" i.d., 13% Carbowax 20 M TPA on Gas Chrom Q, oven temp. 205°C) and determined with a nitrosamine-specific chemiluminescence detector (TEA detector)[2] (sensitivity better than 0.0001 mg/kg). The identity of the nitrosamines was confirmed on combination of gas chromatography and high-resolution mass spectrometry (Varian MAT 311A) at a resolution of $R = 15000$ by precision measurement of the mass of the molecular ion.

The occurrence of even slight amounts of the extremely carcinogenic nitrosamines[3] in commercial material make protective measures imperative during their handling, especially in view of their volatility. Just a single dose of 1.25 mg/kg body weight produces malignant tumors in rats[4]. Moreover, the nitrosamines can appear in the reaction products of such amines, *e.g.* in drugs and pesticides[5]. Hence safety precautions

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

appear urgently required. Studies on the origin of these nitrosamine contaminants should also lead to their partial or complete elimination.

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CAS Registry numbers:
Amines in Table 1 (from top to bottom): 124-40-3; 506-59-2; 109-89-7; 142-84-7; 108-18-9; 111-92-2; 110-96-3; 2050-92-2; 143-16-8; 110-89-4; 123-75-1; 121-44-8

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Ternary Rhenium Sulfides with $[Re_6S_8]$-Clusters

By *Manfred Spangenberg* and *Welf Bronger*[*]

We have been able to synthesize ternary sulfides of general composition $A_xM_yS_z$, where A = alkali metal and M = transition metal, with the elements:

Mn	Fe	Co	Ni	Cu
			Pd	Ag
			Pt	

In all cases, X-ray crystallographic investigations on single crystals gave collective structures in which chain or layer arrays of transition metal atoms are separated from alkali metals by their sulfur environments[1]. Experiments aimed at the preparation of analogous compounds with the usual platinum metals and with gold met without success, but we were able to synthesize the corresponding rhenium compounds. Alkali metal carbonates react with elemental rhenium in an H_2S atmosphere at 800 °C. After *ca.* 20 h well-formed lustrous bluish black crystals (red in transmitted light) of the compounds $Cs_4Re_6S_{13}$, $K_2Re_3S_6$, and $Na_2Re_3S_6$ are obtained. Structure investigations on single crystals of the cesium and potassium compounds showed that the transition metal atoms are not coupled one- or two-dimensionally in layers or chains *via* the coordinated sulfur atoms—as previously reported—but that $[Re_6S_8]$-clusters occur as structural units. Six rhenium atoms form an almost regular octahedron with Re—Re distances of 2.61(1) Å. The eight sulfur atoms are arranged over the octahedron surface. Further S atoms or S_2 groups couple the $[Re_6S_8]$ units *via* the Re atoms. The alkali metal atoms are intercalated in the interstices of these skeletal structures.

Figures 1 and 2 reproduce schematically the linkages of the $[Re_6S_8]$-clusters in two different structural types. For the different stoichiometries there are thus the following formulas:

$Cs_4Re_6S_{13} \triangleq Cs_4[Re_6S_8]S \quad S_{2/2}(S_2)_{3/2}$
$K_2Re_3S_6 \triangleq K_4[Re_6S_8]S_{4/2}\,(S_2)_{2/2}$

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According to previous findings $Na_2Re_3S_6$ is isotypic with the corresponding potassium compound (cf. also Table 1). We have also been able to synthesize a rubidium compound, which is currently under investigation.

Table 1. Measured values of the monoclinic unit cells of ternary rhenium sulfides. The lattice constants *a*, *b*, *c*, are in Å units and β in degrees (standard deviations 0.01 Å and 0.1°, respectively).

	a	*b*	*c*	β	Space group
$Cs_4Re_6S_{13}$	13.72	17.68	10.13	100.8	$P2_1/n$
$K_2Re_3S_6$	16.53	9.69	11.85	91.07	C2/c
$Na_2Re_3S_6$	16.10	9.52	11.61	91.03	C2/c

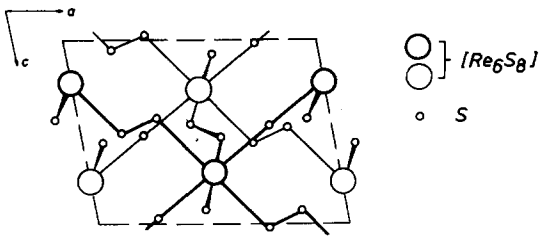


Fig. 1. $Cs_4Re_6S_{13}$: Structure of the $\{[Re_6S_8]S\ S_{2/2}\ (S_2)_{3/2}\}^{4-}$ skeleton. The mass centers of the $[Re_6S_8]$ clusters symbolized by thick circles are each shifted about *b*/2 relative to those represented by thin circles.

Cluster compounds containing M_6 units have so far not been reported in the chemistry of rhenium. $[M_6X_8]$ structural units, in particular with M = Mo or W and X = halogen, have

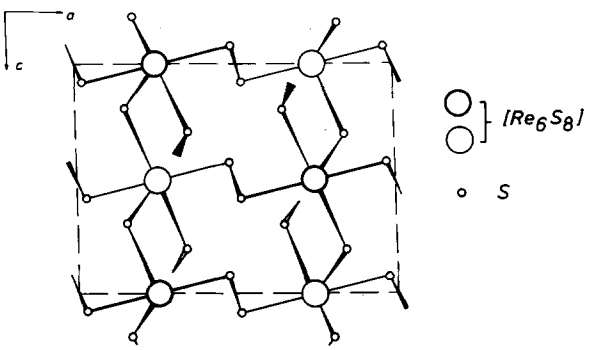


Fig. 2. $K_2Re_3S_6$: Structure of the $\{[Re_6S_8]S_{4/2}\ (S_2)_{2/2}\}^{4-}$ skeleton. The mass centers of the $[Re_6S_8]$ clusters symbolized by thick circles are each shifted about *b*/2 relative to those represented by thin circles.

been observed. In the so-called Chevrel phases, which have attracted interest because of their superconducting properties, $[Mo_6S_8]$ clusters are found to be characteristic structural units[2].

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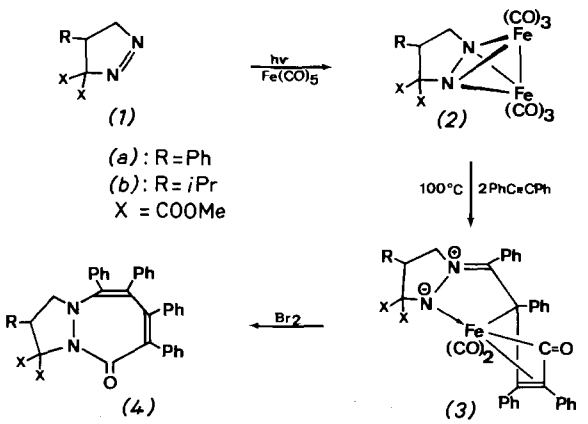
CAS Registry numbers:
$Cs_4Re_6S_{13}$, 66303-37-5; $K_2Re_3S_6$, 66303-36-4; $Na_2Re_3S_6$, 66303-35-3

[1] *W. Bronger* in *F. Lévy*: Crystallography and Crystal Chemistry of Materials with Layered Structures, Vol. 2. Reidel, Dordrecht 1976, p. 93.
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Synthesis of 1,2-Diazepin-3-one Derivatives by Reaction of Alkynes with the N=N Group Coordinated to $Fe_2(CO)_6$[1]

By *Bärbel Ulbrich* and *Horst Kisch*[*]

Complexes of type *(2)* contain a reactive diazene group which can undergo thermal and photochemical reactions with alkynes to form tricyclic organoiron compounds *(3)*[2]. We now wish to report the transformation of these "double addition products" into the hitherto unknown[3] 1,2-dihydro-1,2-diazepin-3-one derivatives *(4)*.



Starting from the 1-pyrazolines *(1a)* or *(1b)*, the corresponding complexes *(3)* can be prepared in 40—50% yield[2]. Oxidative decomposition of, *e.g.*, *(3a)* with bromine in glacial acetic acid/methylene chloride gives 2 mol of CO per mol of *(3a)* and, after column chromatography, a 60% yield[4] of colorless crystals of *(4a)*. Elemental analysis and the mass spectrum (M^+ at $m/e=646$) confirm the composition; the IR spectrum (CCl_4) contains not only the ν(CO) band of the methoxycarbonyl groups at 1730 cm^{-1} but also an intense absorption at 1640 cm^{-1}, which agrees well with the ν(CO) value of 1650 cm^{-1} for a comparable benzodiazepinone[5]. The ^{1}H-NMR spectrum (CD_2Cl_2, 100 MHz) shows the singlets of the ester methyl groups at $\delta=3.25$ and 3.95, the multiplets of the pyrazoline ring protons at $\delta=3.3$—4.1, and those of the aromatic protons at $\delta=6.75$—7.4. Chemical proof of the two C=C double bonds was obtained for the isopropyl derivative *(4b)* synthesized in the same way: uptake of 2 mol of Br_2 per mol of *(4b)* at 0°C in $CHCl_3$ gives a tetrabromo compound which can be dehalogenated by Zn/dimethyl sulfoxide at room temperature to regenerate *(4b)*. The presence of an N—N bond is evidenced by the nuclear magnetic resonance data, and above all by the result of thermolysis of *(4a)* at 180°C: tetracyclone is accompanied by 1,1-dimethoxycarbonyl-2-phenylcyclopropane and 1,1-dimethoxycarbonyl-2-phenyl-1-propene, which are also formed on thermolysis of the free 1-pyrazoline *(1a)*[6].

The reaction sequence *(1)* → *(4)* provides the first demonstration that diazenes activated by transition metals can react with alkynes by C—N and C—C bond formation to give organic heterocycles. This should also be possible with other reactants such as alkenes or 1,3-dienes; use of other transition metal complexes could lead to the discovery of a catalytic variant of this new synthetic approach.

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Procedure

A solution of Br_2 (0.44 g, 2.76 mmol) in glacial acetic acid/methylene chloride (1:1, 50 ml) is added dropwise to a solution of *(3b)* (1 g, 1.38 mmol) in the same solvent system (50 ml). Excess Br_2 is removed by Na_2SO_3 and the organic product is washed with benzene (3 × 100 ml). After drying and evaporation, column chromatography on Florisil (60—100 mesh) gives some tetracyclone on elution with toluene/ether (2:1), and pure *(4b)* with CH_2Cl_2. Crystallization from CH_2Cl_2/MeOH at room temperature gives colorless crystals of *(4b)* (0.48 g, 57%), m.p. 110—116°C (dec.). Compound *(4a)* is accessible in like manner: 60%, m.p. 207—215°C (dec., lilac coloration).

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CAS Registry numbers:
(3a), 66255-77-4; *(3b)*, 66255-76-3; *(4a)*, 66255-63-8; *(4b)*, 66255-62-7

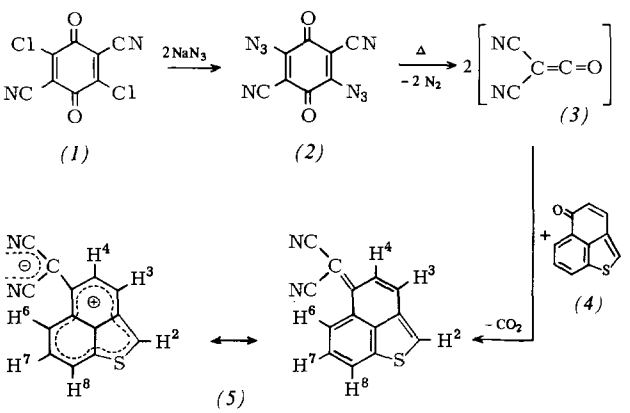
[1] Transition Metal Complexes of Diazenes, Part 11. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 10: *C. C. Frazier III, H. Kisch*, Inorg. Chem., in press.
[2] *A. Albini, H. Kisch*, J. Organomet. Chem. *101*, 231 (1975).
[3] 1,2-Diazepines are reviewed by *M. Nastasi*, Heterocycles *4*, 1509 (1976).
[4] Use of cerium(IV) ammonium nitrate instead of bromine gives 3 mol of CO and a mixture of products which was not further examined.
[5] *N. Dennis, A. R. Katritzky, E. Lunt, M. Ramaiah, R. L. Harlow, S. H. Simonsen*, Tetrahedron Lett. *1976*, 1569.
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Dicyanoketene[**]

By *Richard Neidlein* and *Ernst Bernhard*[*]

Dedicated to Professor Adolf Butenandt on the occasion of his 75th birthday

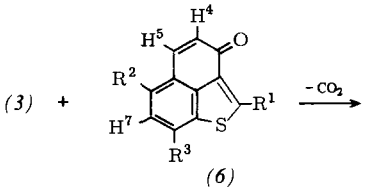
We have synthesized dicyanoketene *(3)*—previously unknown!—from 2,5-diazido-3,6-dicyano-1,4-benzoquinone *(2)* which in turn is formed under special conditions from 2,5-dichloro-3,6-dicyano-1,4-benzoquinone *(1)*[1] and sodium azide in tetrahydrofuran (yield 75%). Alkoxycarbonylcyanoketenes[2] are not accessible by an analogous route. The highly reactive ketene *(3)* could not be trapped by alcohols, amines, *etc.*, for these compounds react with *(2)* itself by substitution of the azide group, and only trapping reactions with polarized ketones were initially considered. Among other compounds, we used thiapseudophenalenones *(4)* and *(6a)*—*(6c)*.



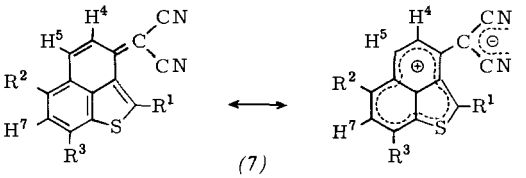
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[**] This work was supported by the Fonds der Chemischen Industrie and by the Deutsche Forschungsgemeinschaft.

If *(2)* is subjected to thermal decomposition[3] in the presence of the thiapseudophenalenones *(4)*[4] and *(6a)—(6c)*[5], then dicyanoketene *(3)* reacts to form the otherwise inaccessible thiapseudophenafulvenes *(5)* and *(7a)—(7c)*;



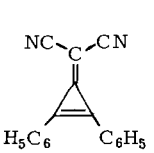
(6)



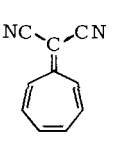
(7)

(a), $R^1 = R^2 = R^3 = H$; *(b)*, $R^1 = CH_3$; $R^2 = R^3 = H$; *(c)*, $R^1 = H$; $R^2 = R^3 = Cl$

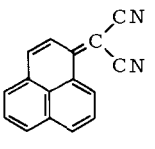
the paramagnetic shift of the ^{1}H-NMR signals suggests polarization of these products.



(8)



(9)



(10)

The dicyanofulvenes *(8)*[6] (yield: 26 %), *(9)*[7] (yield: 20 %), and *(10)*[8] (yield: 37 %) which we obtained from dicyanoketene *(3)* and diphenylcyclopropenone, tropone, and phenalenone were identical with authentic material in their physicochemical and spectroscopic properties.

Table 1. Physical properties of compounds *(5)* and *(7a)—(7c)*.

(5): m.p. 253—254 °C; yield: 54 %; $M^+ = 234.0247$ (calc.: 234.0251); ^{1}H-NMR ($CDCl_3$): $\delta = 8.06$ (s, H^2), 7.49 (d, H^3, $J = 9.7$ Hz), 7.45 (d, H^4, $J = 9.7$ Hz), 9.13 (d of d, H^6, $J_{ortho} = 7.9$ Hz, $J_{meta} = 0.17$ Hz), 7.71 (t, H^7, $J_{ortho} = 7.9$ Hz, $J_{ortho} = 7.9$ Hz), 8.81 (d of d, H^8, $J_{ortho} = 7.9$ Hz, $J_{meta} = 0.7$ Hz); UV (CH_3CN): $\lambda_{max} = 456$ nm ($\varepsilon = 24760$), 305 (4430), 273 (5760), 242 (10000)

(7a): m.p. 222—223 °C; yield: 48 %; $M^+ = 234.0247$ (calc.: 234.0251); ^{1}H-NMR ([D$_6$]-acetone): $\delta = 9.64$ (s, H^2), 7.42 (d, H^4, $J = 9.4$ Hz), 7.87 (d, H^5, $J = 9.4$ Hz), 7.93 (d of d, H^6, $J_{ortho} = 7.5$ Hz, $J_{meta} = 1.2$ Hz), 7.77 (t, H^7, $J_{ortho} = 7.5$ Hz, $J_{ortho} = 7.5$ Hz), 8.31 (d of d, H^8, $J_{ortho} = 7.5$ Hz, $J_{meta} = 1.2$ Hz); UV (CH_3CN): $\lambda_{max} = 458$ nm ($\varepsilon = 16050$), 323 (3105), 264 (18220), 239 (10490)

(7b): m.p. 188—189 °C; yield: 3.2 %; $M^+ = 248.0404$ (calc.: 248.0408); ^{1}H-NMR ([D$_6$]-acetone): $\delta = 3.01$ (s, CH_3), 7.55 (d, H^4, $J = 9.5$ Hz), 7.86 (d, H^5, $J = 9.5$ Hz), 7.91 (d of d, H^6, $J_{ortho} = 7.6$ Hz, $J_{meta} = 1.2$ Hz), 7.70 (t, H^7, $J_{ortho} = 7.6$ Hz, $J_{ortho} = 7.6$ Hz), 8.23 (d of d, H^8, $J_{ortho} = 7.6$ Hz, $J_{meta} = 1.2$ Hz); UV (CH_3CN): $\lambda_{max} = 457$ nm ($\varepsilon = 19160$), 324 (5350), 267 (20760), 248 (18650)

(7c): m.p. 270 °C (dec.); yield: 27 %; $M^+ = 301.9468$ (calc.: 301.9472); ^{1}H-NMR ([D$_6$]-DMSO): $\delta = 9.60$ (s, H^2), 7.32 (d, H^4, $J = 9.5$ Hz), 7.85 (d, H^5, $J = 9.5$ Hz), 7.98 (s, H^7); UV (CH_3CN): $\lambda_{max} = 480$ nm ($\varepsilon = 18170$), 459 (19340), 325 (2120), 272 (21610), 246 (12830)

Experimental

Synthesis of (2): A 25 % aqueous solution of sodium azide (2.6 ml, 10 mmol) is added to a stirred solution of *(1)* (1.00 g, 4.40 mmol) in THF (20 ml) at −5 °C. The product is precipitated from the red solution by addition of ice-water (400 ml). The orange crystals are filtered off after a few minutes, the filter crucible being cooled with ice. The crystals are washed several times with cold ether, dried *in vacuo*, and stored in a refrigerator with exclusion of moisture, yield: 780 mg (74 %) of *(2)*; *IR* (KBr): 2240, 2210 (C≡N), 2155, 2100 (N_3), 1660 (C=O), 1560 cm^{-1} (C=C); UV (CH_3CN): $\lambda_{max} = 334$ nm ($\varepsilon = 25300$), 260 (17300), 226 (15000).

Synthesis of (5), (7a)—(7c), (8)—(10): A 0.25 mmol sample of *(4)*, *(6a)—(6c)*, diphenylcyclopropenone, tropone, or phenalenone and *(2)* (90.0 mg, 0.375 mmol) are refluxed in anhydrous benzene (25 ml) under N_2 for 4 h. The evaporated solution is applied to a silica gel PLC plate (PSC Kieselgel, "Merck") and developed with dichloromethane. The reddish fractions (yellow in the case of *(9)*) are extracted with dichloromethane (Soxhlet) and the solutions carefully evaporated. The physical data of *(5)* and *(7a)—(7c)* are listed in Table 1.

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German version: Angew. Chem. *90*, 395 (1978)

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Azoalkanes by Anodic Oxidation of Anions of *N,N'*-Dialkylsulfamides[**]

By *Reinhold Bauer* and *Hartmut Wendt*[*]

Hypochlorite oxidation of ammonia, alkylsulfamides or geminal diamines is the usual reaction path to hydrazine, substituted hydrazines or azoalkanes, respectively[1]. The anodic oxidation of anions of primary and secondary amines in aprotic solvents opens another route to N—N-coupling products[2]. This electrochemical method can also be used for the anions of *N,N'*-dialkylsulfamides *(1)* and thus offers the possibility of carrying out anodic N—N-coupling in *protic solvents*, in a reaction which is easy to perform and which affords azoalkanes in about 90 % yield with attractive current efficiencies. Table 1 lists the anodic half-wave potentials of some sulfamides *(1)* and their monoanions *(2)*. The anions are generally oxidized in a one-electron step at potentials which are 600 to 800 mV more negative than the half-wave potentials of the corresponding sulfamides. Oxidation products are the azoalkanes *(4)*. Table 2 lists mass yields and current efficiencies for the potentiostatic oxidation of *(2)*.

Table 1. Anodic half-wave potentials of *N,N'*-dialkylsulfamides and their anions in methanol at a carbon electrode with 0.1 M *n*-Bu_4BF_4 as supporting electrolyte ($E_{1/2}$ [mV] measured *vs.* aqueous SCE).

R	$RHN—SO_2—NHR$ *(1)*	$RHN—SO_2—NR^{\ominus}Li^{\oplus}$ *(2)*
n-Butyl	1655	850
t-Butyl	1650	1000
Cyclohexyl	1520	880
Adamantyl	1510	910

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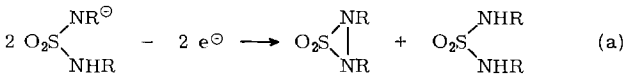
[**] This work was supported by the Deutsche Forschungsgemeinschaft.

Table 2. Mass yields and current efficiencies for some reactions *(2)* → *(4)* in methanol at C- and Pt-electrodes.

RN=NR *(4)* R	Mass yields [%] Carbon	Platinum	Current yields [%] [a] Carbon	Platinum
n-Butyl	88	94	68	72
t-Butyl	81	84	63	62
Cyclohexyl	90	93	74	77
Adamantyl	78	79	61	60

[a] Assuming consumption of two electrons per molecule of azoalkane in accordance with equations (a) and (b).

A detailed investigation shows that the cyclic thiadiaziridine 1,1-dioxide *(3)* is formed as a primary oxidation product of the formal one-electron oxidation (being in fact a sequence of charge transfer, deprotonation and second charge transfer) [Eq. (a)]. In the case of the *N,N'*-diadamantyl derivative, after the electrolysis *(3)* could be isolated in small amounts (10%) besides the 1,1'-azoadamantane. The three-membered heterocycles with spatially less demanding *N*-alkyl groups slowly decompose in a well known thermal reaction to SO_2 and the azoalkanes *(4)*[3] [Eq. (b)].



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



(4) (b)

Anodic oxidation of *N,N'*-dialkylsulfamides in the absence of base leads merely to fragmentation and not to N—N-coupling. Since azoalkanes can easily be converted into hydrazines by catalytic hydrogenation the described method provides access also to symmetrically substituted hydrazines[4]. This new anodic synthesis is based on direct anodic conversion of N-anions in protic solvents and avoids the use of chlorine or hypochlorite as oxidants.

Experimental

N,N'-dicyclohexylsulfamide (5.20 g, 0.02 mol) is dissolved in dry methanol (100 ml) and converted into the lithium salt by addition of an equimolar amount of Li-methoxide. This solution is oxidized at controlled potential at a carbon electrode in a divided cell at 273 K under a N_2 atmosphere. After consumption of 0.04 F the solvent is removed and the residue is extracted twice with 50 ml of *n*-pentane. Subsequent drying of the combined extracts over Na_2SO_4 and removal of the solvent by evaporation affords 2.73 g (90% mass yield and 74% current yield) azocyclohexane, m.p. 307 K (Ref.[5] 307.5 K). The product was identified by comparing its spectroscopic data (MS, IR, UV, ^{1}H-NMR with those of an authentic sample prepared according to the procedure of *Ohme et al.*[6].

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CAS Registry numbers:
(1), R = *n*-butyl, 763-11-1; *(1)*, R = *t*-butyl, 13952-67-5; *(1)*, R = cyclohexyl, 14041-87-3; *(1)*, R = adamantyl, 42399-75-7; *(2)*, R = *n*-butyl, 66255-51-4; *(2)*, R = *t*-butyl, 66255-52-5; *(2)*, R = cyclohexyl, 66255-53-6; *(2)*, R = adamantyl, 66255-54-7; *(4)*, R = *n*-butyl, 2159-75-3; *(4)*, R = *t*-butyl, 927-83-3; *(4)*, R = cyclohexyl, 2159-74-2; *(4)*, R = adamantyl, 21245-62-5

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Facile Preparation of Cyclooctatetraene from 1,5-Cyclooctadiene by Metalation and Oxidation

By *Wolfgang Gausing* and *Günther Wilke*[*]

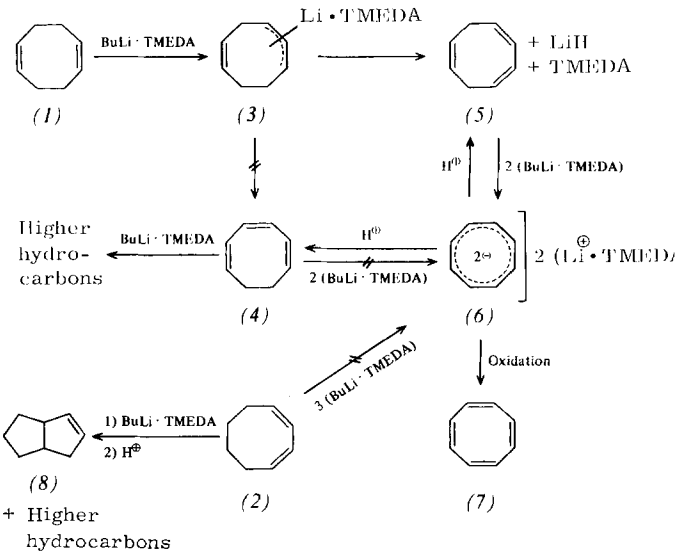
Metalation of olefins is attracting increasing interest; particular mention should be made of the formation of the trimethylenemethane dianion from isobutene[1] and of the cycloheptatrienyl trianion from various C_7-di- and tri-olefins[2]. 1,4-Cyclooctadiene is transformed into bicyclo[3.3.0]oct-2-ene by lithiation and protolysis[3].

We now wish to report the metalation of 1,5-cyclooctadiene *(1)*, of 1,3-cyclooctadiene *(2)*, and of 1,3,5-cyclooctatriene *(4)* and its 1,3,6 isomer *(5)*. The 1,5-diene *(1)* was expected to react with *n*-butyllithium-tetramethylethylenediamine[4] (BuLi·TMEDA) in the molar ratio 1:1 to give the allyl anion *(3)*. On protolysis of the product, however, we obtained not only *(1)* and its isomers but also the trienes *(4)* and *(5)* and hydrogen. The product apparently contained $Li_2(C_8H_8)$[5] and LiH.

Reaction of *(1)* with BuLi·TMEDA in a ratio of 1:3 gives LiH and crystalline $Li_2(C_8H_8)\cdot 2$TMEDA *(6)* in practically quantitative yield: the latter product affords cyclooctatetraene *(7)* in 90—95% yield (based on *(1)*) on oxidation with $CdCl_2$[5b, 6].

In an attempt to simplify this new synthesis of cyclooctatetraene for preparative purposes we have tried other metalation and oxidizing agents. A particularly suitable procedure proved to be the initial reaction of *(1)* with phenylsodium in the presence of TMEDA followed by oxidation with dry oxygen. Formation of *(7)* is accompanied by a mixture of sodium peroxide and hyperoxide[7].

The results of reactions of *(2)*, *(4)*, and *(5)* with *n*-butyllithium helped to elucidate the reaction mechanism: under the



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same conditions neither 1,3-cyclooctadiene nor 1,3,5-cyclooctatriene can be converted in significant amounts into *(6)*, 1,3,6-cyclooctatriene on the other hand reacts smoothly to give this product; addition of the BuLi-reagent to *(2)* and *(4)* does occur and in the case of *(2)* bicyclo[3.3.0]oct-2-ene *(8)* is formed. This suggests that *(1)* and BuLi·TMEDA initially form *(3)*, which is transformed into *(5)* by loss of LiH and TMEDA. Double metalation of *(5)* yields the intermediate *(6)*.

Procedure

Compound *(1)* (12 ml, 10.6 g, 98 mmol) is added to C_6H_5Na[8] (0.31 mol) in olefin-free pentane (150 ml) and TMEDA (95 ml), and the mixture is stirred under reflux for 20 h. A slow current of dry O_2 is then passed over the well stirred mixture at −5 °C for *ca.* 24 h. After filtration[7] the solution is vacuum distilled, freed from TMEDA with 5 N HCl, neutralized, and dried. GC analysis reveals 1.5 % (163 mg, 1.5 mmol) of *(8)* and 78.5 % (8 g, 76.9 mmol) of *(7)*, based on quantitatively consumed *(1)*. The remainder of *(1)* is present as oligomerization product in the distillation residue.

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CAS Registry numbers:
(1), 111-78-4; *(2)*, 1700-10-3; *(4)*, 1871-52-9; *(5)*, 3725-30-2; *(7)*, 629-20-9; *(8)*, 5549-09-7

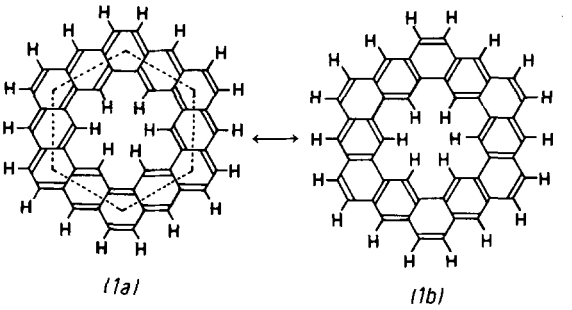
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[6] As recently reported, *(1)* can be transformed into *(7)*, albeit in poor yield by reaction with potassium and subsequent oxidation: *W. J. Evans, A. L. Wayda, C.-W. Chang, W. M. Cwirla*, J. Am. Chem. Soc. *100*, 333 (1978).
[7] Caution! NaO_2 decomposes spontaneously with evolution of O_2 on exposure to water. The filter cake is sensitive to heat and shock when dry.
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Benzenoid *versus* Annulenoid Aromaticity: Synthesis and Properties of Kekulene[1]

By *François Diederich* and *Heinz A. Staab*[*]

In 1965, first attempts to prepare the hydrocarbon *(1)* were reported[2]. Then, at the centennial of *Kekulé*'s benzene formula, this compound which may be regarded as a "superbenzene" on account of its planar cyclic conjugation and D_{6h} symmetry was given the name "kekulene"[2, 3]. *(1)* was of interest in connection with investigations to experimentally define benzenoid as against annulenoid aromaticity: on the one hand, *(1)* can be formulated as a combination of two [4*n*+2]annulenes—[18]annulene inside, [30]annulene outside—bridged by radial single bonds *(1a)*, and on the other, as a regular benzenoid system with a closed circle of angularly annellated benzene rings *(1b)*. Since *(1)*, in this respect a representative of a new class of aromatic compounds, has an intramolecular cavity containing hydrogen atoms it should be possible to decide by proton resonance whether an annulenoid diatropism in the macrocyclic system can compete successfully with ring-current induction within the benzenoid subunits.

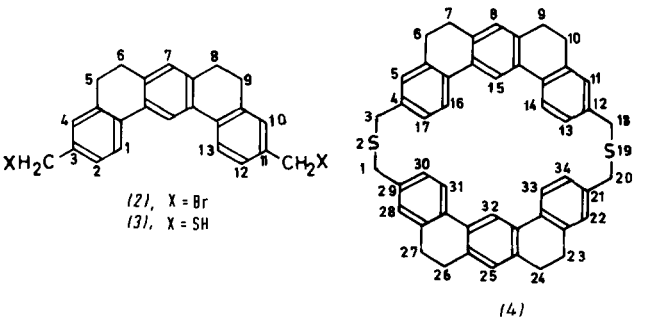
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(1a) *(1b)*

In an attempt to synthesize *(1) via* a very involved and tedious route *Vögtle* and *Staab*[4] were able to show, on the basis of a mass spectrometric analysis, that the desired compound was probably formed, albeit in minute and unisolable amounts. Since preparation of *(1) via* such a route seemed impossible all further efforts were abandoned 10 years ago. Attempts by *Tenny et al.*[5] to prepare *(1)*, which they named '[12]coronaphene' apparently were likewise unsuccessful. Newly developed methods for C...C coupling in macrocyclic systems, especially by sulfur extrusion from dithia[3.3]phanes, prompted us now to resume our efforts to synthesize *(1)*.

The first steps of the synthesis followed, with minor modifications, those of the previously reported synthesis of 5,6,8,9-tetrahydrodibenzo[*a,j*]anthracene[4], whose bromomethylation according to the procedure used for 9,10-dihydrophenanthrene[6], led to the bis(bromomethyl) derivative *(2)*[7] in 50% yield. After conversion of *(2)* into the bis(mercaptomethyl) derivative *(3)*[7] [thiourea method; 75 % yield, m.p. 243 °C (corr.)], *(2)* and *(3)* were cyclized to 6,7,9,10,23,24,26,27-octahydro-2,19-dithia[3.3](3,11)dibenzo[*a,j*]anthracenophane[8] *(4)* [dilution apparatus of *Vögtle*; solutions of *(2)* and *(3)* in benzene (each 5.3 mmol in 3500 ml) added dropwise and simultaneously within 72 h into a boiling mixture of 1000 ml benzene, 1000 ml ethanol (95 %) and 4 g potassium hydroxide; 55 % yield]. *(4)*[7]: yellowish platelets, m.p. 291 °C (corr.); ^{1}H-NMR (360 MHz, $CDCl_3$): $\delta = 2.70$ (s, 16H, H-6,7,9,10,23,24,26,27), 3.82 (s, 8H, H-1,3,18,20), 6.73 (dd, $J = 8$ and 1.8 Hz, 4H, H-13,17,30,34), 6.91 (s, 2H, H-8,25), 6.94 (d, $J \approx 1.8$ Hz, 4H, H-5,11,22,28), 7.40 (d, $J = 8$ Hz, 4H, H-14,16,31,33), 7.83 (s, 2H, H-15,32).

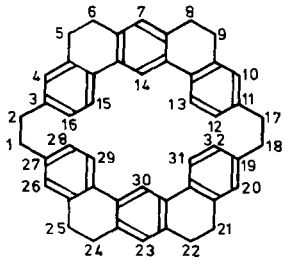


(2), X = Br
(3), X = SH

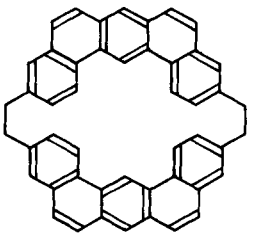
(4)

Irradiation of *(4)* in trimethyl phosphite (450 W Hg high-pressure lamp, 2 h, under N_2) led in 60% yield to 5,6,8,9,21,22,24,25-octahydro[2.2](3,11)dibenzo[*a,j*]anthracenophane *(5)*[7]: colorless needles, m.p. 462–464 °C. *(5)*, which had already been obtained in very unsatisfactory yield (1.5%) from *(2)* by a Wurtz reaction (phenyllithium, ether/benzene)[4], was dehydrogenated with 2,3-dichloro-5,6-

dicyano-1,4-benzoquinone (DDQ) [24 h, boiling benzene, 80 % yield] to *(6)*[7]: pale yellow needles, m.p. 490—495 °C (dec.); MS: $m/e = 608$ (M^+, base peak), 304 (70 %). The rigid steplike structure of the molecule is confirmed by the absorption of the methylene bridges and the upfield shift of the adjacent internal aromatic protons in the ^{1}H-NMR spectrum (360 MHz, $CDCl_3$, 45 °C) [$\delta = 2.69$ and 3.33 (each 'd', $J \approx 9$ Hz, for axial and equatorial H-1,2,17,18, resp.), 5.76 (dd, $J = 9$ and 2 Hz, 4H, H-12,16,28,32), 7.68 and 7.81 (AB, $J = 8$ Hz, 8H, H-5,9,21,25 and H-6,8,22,24), 7.72 (d, $J \approx 2$ Hz, H-4,10,20,26), 8.04 (d, $J = 9$ Hz, 4H, H-13,15,29,31), 8.31 (s, 2H, H-7,23), 9.56 (s, 2H, H-14,30)][9]. All attempts to achieve the internal ring closure in *(6)* and the dehydrogenation to *(1)* have so far remained unsuccessful.

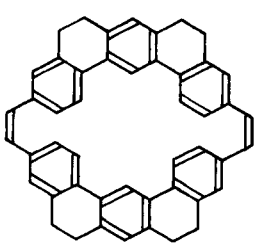


(5)

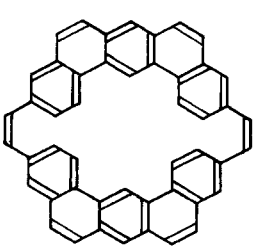


(6)

Subjection of the bis-sulfonium salt formed on reaction of the dithiaphane *(4)* with methyl fluorosulfonate (in methylene chloride, 95 % yield) to Stevens rearrangement (potassium *tert*-butoxide, tetrahydrofuran, 12 h, 20 °C, under N_2, 60 % yield), renewed methylation (methyl fluorosulfonate, methylene chloride, ≈ 90 % yield) and elimination (potassium *tert*-butoxide, tetrahydrofuran, 12 h, 20 °C, 9 % yield) afforded 5,6,8,9,21,22,24,25-octahydro[2.2](3,11)dibenzo[*a*,*j*]anthracenophanediene *(7)*[7]: pale yellow needles, m.p. 472 °C (dec.); ^{1}H-NMR (360 MHz, $CDCl_3$): $\delta = 2.883$ (s, 16H, H-5,6,8,9,21,22,24,25), 6.575 (dd, $J = 8.28$ and 1.68 Hz, 4H, H-12,16,28,32), 6.745 (s, 4H, H-1,2,17,18), 7.098 (d, $J = 1.68$ Hz, 4H, H-4,10,20,26), 7.114 (s, 2H, H-7,23), 7.365 (d, $J = 8.28$ Hz, 4H, H-13,15,29,31), 7.658 (s, 2H, H-14,30).—Dehydrogenation of *(7)* with DDQ (boiling benzene, 20 h, 66 %) yielded the dibenzo[*a*,*j*]anthracenophanediene *(8)*[7]: yellow needles, m.p. > 520 °C (subl.); MS: M^+ calc. for $C_{48}H_{28}$ 604.2191, obs. 604.2197; ^{1}H-NMR (360 MHz, [D_5]nitrobenzene, 80 °C): $\delta = 7.075$ (s, 4H, H-1,2,17,18), 7.119 (d, $J = 8.7$ Hz, 4H, H-12,16,28,32), 7.782 (br. s, 4H, H-4,10,20,26), 7.737 and 7.793 (AB, $J = 8.95$ Hz, 8H, H-5,9,21,25 and H-6,8,22,24), 8.141 (s, 2H, H-7,23), 8.602 (d, $J = 8.7$ Hz, 4H, H-13,15,29,31), 9.742 (s, 2H, H-14,30) [numbering of carbon atoms cf. formula *(5)*].

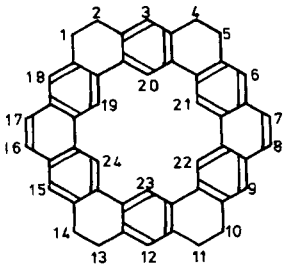


(7)



(8)

In contrast to *(8)*, an easy photo-cyclodehydrogenation was possible with *(7)* in which two *cis*-stilbene units are present: short irradiation (10 min, 300 W Osram-Ultra-Vitalux lamp) in benzene in the presence of iodine afforded the octahydro derivative *(9)*[7], the first compound with the carbon skeleton of kekulene, in 70 % yield: m.p. > 620 °C, pale yellow needles (from nitrobenzene), difficultly soluble in all solvents. MS: $m/e = 608$ (20 %, M^+), 607 (8), 606 (14), 605 (5), 604 (14), 603 (9), 602 (35), 601 (55), 600 (base peak, corresponding to *(1)*) and the doubly and triply charged ions therefrom at $m/e = 300$ (82) and 200 (7). ^{1}H-NMR (360 MHz, [D_5]nitrobenzene/arsenic trichloride, 1:3, 685 scans): $\delta = 3.11$—3.27 (AA'BB', 16H, H-1,5,10,14 and H-2,4,11,13), 7.26 (s, 2H, H-3,12), 7.74 and 7.77 (each s, 4H, H-7,8,16,17 and H-6,9,15,18), 9.19 (s, 2H, H-20,23), 9.67 (s, 4H, H-19,21,22,24).



(9)

Because of the low solubility of *(9)* the dehydrogenation with DDQ required rather drastic conditions (1,2,4-trichlorobenzene, 100 °C, 3 d). Kekulene *(1)* was formed in 80 % yield. With its extreme insolubility in solvents of all kinds, *(1)* is certainly outstanding among hydrocarbons of comparable molecular weight: for recrystallization, for example, 350 ml 1-methylnaphthalene at the boiling point (245 °C) dissolved 10 mg *(1)*, or 100 ml boiling 1,2,4-trichlorobenzene (b.p. 214 °C) about 1 mg *(1)*. Kekulene *(1)*[7], greenish-yellow microcrystals, m.p. > 620 °C, can be sublimed at 500 °C/10^{-3} torr. MS: M^+ calc. for $C_{48}H_{24}$ 600.1858, obs. 600.1878. In the mass spectrum, which is extraordinarily poor in fragment peaks, there appear besides the molecular peak $m/e = 600$ (100 %) the doubly and triply charged molecular ions at $m/e = 300$ (43 %) and 200 (7 %); above the molecular peak and its ^{13}C-peaks with intensities expected for C_{48} no further peaks are observed (up to $m/e = 2000$, temperature of the ionic source up to 400 °C)[10]. The complete dehydrogenation of *(9)* is also shown by the IR spectrum (KBr) in which the aliphatic ν(C—H) absorptions have disappeared; the spectrum shows only aromatic ν(C—H) absorptions (3007 and 3020 cm^{-1}) and, in accord with the high molecular symmetry, is very poor in vibration absorptions.

The electronic spectrum of *(1)* ($8 \cdot 10^{-7}$ molar solution in 1,2,4-trichlorobenzene) shows the following absorptions: λ_{max} 388 nm (lg ε 4.22), 347 (sh, 4.74), 326 (4.93). Solutions of *(1)* exhibit intense green fluorescence; in 1,2,4-trichlorobenzene a fluorescence emission is observed from about 400 to 550 nm with maxima at 420 and 435 nm (excitation at 365 nm). Under the same conditions a phosphorescence emission is observed around 590 nm with a half life of 0.6 s at −196 °C[11].

The extreme insolubility of *(1)* made the recording of a ^{1}H-NMR spectrum extraordinarily difficult. In the first usable spectra (80 MHz) of a saturated solution of *(1)* in [D_3]-1,3,5-trichlorobenzene at 215 °C after about 50000 scans three signals were observed reproducibly at $\delta = 7.94$, 8.37 and 10.45 in the intensity ratio of 2:1:1[12]. According to these results, there is no signal shifted strongly upfield as would be expected for the internal protons in the case of a synchronous induction of diamagnetic ring-currents in a double annulene system. On the contrary, intensity ratios and comparison with the ^{1}H-NMR data of compounds *(5)* to *(9)* lead to the

assignment of the signal at $\delta = 7.94$ to the twelve equivalent protons H-1,2,4,5,7,8..., of the absorption at $\delta = 8.37$ to the second group of equivalent external protons H-3,6,9,12,15,18 and of the signal at $\delta = 10.45$ to the six internal protons H-19,20,21,22,23,24 [numbering as in *(9)*]. The peculiar downfield shift just of the internal protons of *(1)* is taken as a strong experimental argument against the dominance of an annulenoid ring-current in the macrocyclic system and in favor of a strong coupling between the inner and outer perimeters according to the benzenoid formulation *(1b)*. This result is inconsistent with calculations of the diamagnetic anisotropy for *(1)* using the semi-classical approach of *Pauling*[13a]; it agrees qualitatively, however, with more recent MO calculations[13].

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CAS Registry numbers:
(1), 15123-47-4; *(2)*, 66183-91-3; *(3)*, 66183-90-2; *(4)*, 66183-89-9; *(5)*, 19576-05-7; *(6)*, 66183-88-8; *(7)*, 66183-87-7; *(8)*, 21273-84-7; *(9)*, 66183-86-6

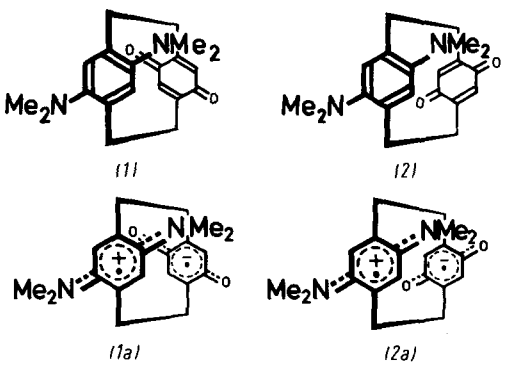
[1] Conjugation in Macrocyclic Systems, Part 27.—Part 26: *U. E. Meissner, A. Gensler, H. A. Staab*, Tetrahedron *1977*, 3.
[2] *H. A. Staab*, Plenary Lecture at the Annual Meeting, Gesellschaft Deutscher Chemiker (Kekulé Centennial) in Bonn on 14.9.1965.
[3] The naming of *(1)* as a polycyclic system according to the IUPAC rules on nomenclature leads to an extraordinarily complicated name which does not give any direct information about structure and symmetry of the molecule (see also [4]).
[4] *F. Vögtle, H. A. Staab*, Chem. Ber. *101*, 2709 (1968).
[5] *K. Burri, W. Jenny*, Helv. Chim. Acta *50*, 1978, 2542 (1967); *W. Jenny, R. Paioni*, Chimia *22*, 248 (1968); *23*, 41 (1969); Helv. Chim. Acta *53*, 141 (1970); *P. Baumgartner, R. Paioni, W. Jenny, ibid. 54*, 266 (1971).
[6] *H. A. Staab, M. Haenel*, Chem. Ber. *106*, 2190 (1973); cf. also *J. v. Braun*, Ber. Dtsch. Chem. Ges. *70*, 979 (1937).
[7] Elemental analyses, molecular weights and spectroscopic data are in agreement with the structures mentioned.
[8] For the 'phane-nomenclature' cf. *F. Vögtle, P. Neumann*, Tetrahedron *26*, 5847 (1970).
[9] Cf. the results obtained for the sterically similar [2.2](2,7)naphthalenophane: *J. R. Davy, J. A. Reiss*, Aust. J. Chem. *29*, 163 (1976).
[10] We thank Dr. *W. Otting*, Max-Planck-Institut für medizinische Forschung Heidelberg, for the recording of the mass spectra, which for most of the compounds mentioned here was very difficult.
[11] *D. Schweitzer*, unpublished.
[12] We thank Professor *J. Dabrowski* and *D. Griebel* of our Department for the great effort made by them in overcoming the unusual technical difficulties in the ^{1}H-NMR-measurements of *(1)*.
[13] a) *R. McWeeny*, Proc. Phys. Soc. London *A64*, 261, 921 (1951); cf. also *L. Pauling*, J. Chem. Phys. *4*, 673 (1936); b) *G. Ege, H. Fischer*, Tetrahedron *23*, 149 (1967); *G. Ege, H. Vogler*, Theor. Chim. Acta *26*, 55 (1972).

Attempts to Synthesize Zwitterionic Donor-Acceptor Cyclophanes: The Diastereomeric 12,15-Bis(dimethylamino)-[2](2,5)-*p*-benzoquinono[2]paracyclophanes[1]

By *Renate Reimann* and *Heinz A. Staab*[*]

Previous investigations of charge-transfer interactions in donor-acceptor cyclophanes[2] led to the question of the existence of 'paracyclophane-zwitterions' in which, as a consequence of an especially low ionization potential of the donor or a high electron affinity of the acceptor, an electron transfer from donor to acceptor occurs already in the ground state of the molecule. Such paracyclophanes for which the radical cation and the radical anion components would be fixed in close proximity and definite orientation were of interest regarding the interaction between the radical electrons: strong coupling should lead to a singlet (or a triplet?) ground state of the molecule, whereas with weak transanular interaction the single radical ion units of such a molecule should exist in doublet spin states. Furthermore, we wondered whether a zwitterionic structure of donor-acceptor cyclophanes would result in a crystal structure comprising stacked cyclophane moieties where the stacking axis is perpendicular or nearly perpendicular to the cyclophane planes and, therefore, the radical cation side of one cyclophane directly faces the radical anion side of the neighboring molecule. For such lattice structures peculiar anisotropic crystal properties (*e.g.*, changes in electrical conductivity) might be expected.

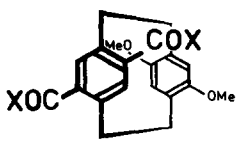
As an effort aimed in this direction we synthesized the donor-acceptor cyclophanes *(1)* and *(2)* in which *p*-benzoquinone as acceptor is combined in pseudo-*ortho* and pseudo-geminal orientations with the especially strong donor *N,N,N',N'*-tetramethyl-*p*-phenylene diamine (TMPD). The zwitterions *(1a)* and *(2a)* corresponding to *(1)* and *(2)*, respectively, would include as components the semiquinone radical anion and the 'Wurster's Blue' radical cation, both of which are known as relatively stable radical ions. Although, in intermolecular CT complexes of TMPD, the formation of radical ions apparently requires acceptors with higher electron affinity (*e.g.*, chloranil)[3], due to the specific interactions in [2.2]paracyclophanes, no definite conclusions could be drawn regarding the stability of the zwitterions *(1a)* and *(2a)* as against *(1)* and *(2)*.



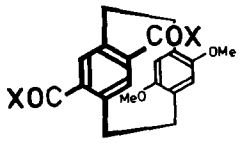
For the syntheses of *(1)* and *(2)*, after the failure of more direct synthetic routes, we had to adopt the multi-step course starting from the diastereomeric 4,7-dimethoxy-12,15-dimethoxycarbonyl[2.2]paracyclophanes *(3)* and *(4)* which had already been synthesized as donor-acceptor cyclophanes previously[11].

Hydrolysis of *(3)* (potassium hydroxide, methanol; 24 h, 97 % yield) afforded the dicarboxylic acid *(5)*[4] (dec. > 320 °C), which on reaction with sulfinyl chloride (chloroform/dimethylformamide; 85 % yield) gave the dichloride *(7)*[4] (m.p. 152 °C). Treatment of *(7)* with sodium azide in acetone/water afforded the diazide *(9)*[4] (dec. > 90 °C, 85 % yield). Subsequent Curtius reaction of *(9)* (boiling toluene, 2 h) led to the diamino derivative which, on account of its extraordinary instability, without further purification and characterization was methylated with methyl iodide/potassium carbonate (methanol, 20 °C, under argon) to pseudo-*ortho*-4,7-dimethoxy-12,15-bis(dimethylamino)[2.2]paracyclophane *(11)*[4] (colorless crystals, m.p. 98 °C, overall yield 31 %).

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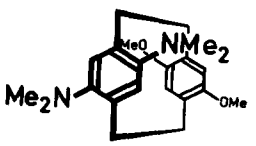


(3), X = OMe
(5), X = OH
(7), X = Cl
(9), X = N_3

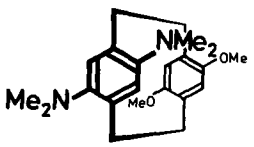


(4), X = OMe
(6), X = OH
(8), X = Cl
(10), X = N_3

Analogously, in the pseudogeminal series, starting from (4) we obtained the dicarboxylic acid (6)[4] (dec. >320°C, 94.5% yield), the dichloride (8)[4] (m.p. 214°C; 88% yield), and the diazide (10)[4] (dec. >114°C; 81% yield). Curtius reaction of (10) and immediate subsequent methylation yielded the pseudogeminal bis(dimethylamino) derivative (12)[4] (pale yellow crystals, m. p. 181°C, overall yield 11%).—For all pairs of diastereomers of the two series the assignment to the pseudo-*ortho* and pseudogeminal structures, respectively, is confirmed by comparison of ^{1}H-NMR data; particularly characteristic is the transannular substituent effect of the methoxy groups which, for the aromatic protons in pseudogeminal positions of the neighboring ring, results in a downfield shift[5].



(11)



(12)

In the following reaction steps the ether cleavage in (11) and (12) and the oxidation to the benzoquinone had to be accomplished under reaction conditions under which the TMPD part of the molecule is not affected. According to model experiments with mixtures of TMPD and hydroquinone dimethylether, this could be achieved by demethylation with methyl magnesium iodide [(11): 190°C, 50 min; (12): 195°C, 75 min] and oxidation with silver oxide in ether. After chromatography on silica gel from toluene/methanol (10:1) and recrystallization from pet. ether (40—60) (1) was obtained in 15.5% yield, and (2) in 18% yield.—(1)[4]: black crystals, m.p. 183°C; MS: M^+ calc. for $C_{20}H_{24}N_2O_2$ 324.1838, obs. 324.1844; ^{1}H-NMR ($CDCl_3$): $\delta = 2.0$—3.7 (m, 8H), 2.67 (s, 12H), 5.93 (s, 2H), 6.14 (s, 2H).—(2)[4]: black crystals, m.p. 204°C; MS: M^+ calc. for $C_{20}H_{24}N_2O_2$ 324.1838, obs. 324.1828; ^{1}H-NMR ($CDCl_3$): $\delta = 2.0$—3.7 (m, 8H), 2.68 (s, 12H), 5.80 (s, 2H), 6.13 (s, 2H).

(1) and (2) show unusually broad absorption bands which extend from about 450 nm through the whole visible region into the near infrared. Long-wavelength initial absorptions and absorption maxima are strongly solvent-dependent and, in general, show a bathochromic shift with increasing polarity of the solvent; a strict correlation with dielectric constants or dipole moments of the solvent is, however, not observed. In the whole region of the long-wavelength absorption the absorption intensity of the pseudogeminal compound is higher by a factor of about 10 than that of the pseudo-*ortho* isomer [(1): $\lambda_{max} = 545$ nm ($\varepsilon = 147$), in cyclohexane; $\lambda_{max} = 595$ nm ($\varepsilon = 160$), in methylene chloride; (2): $\lambda_{max} = 531$ nm ($\varepsilon = 1670$), in cyclohexane; $\lambda_{max} = 577$ nm ($\varepsilon = 1930$), in methylene chloride]. The solvent-dependence of the absorption maxima as well as the orientation dependence of the absorption intensities, similar to those of [2.2]paracyclophane quinhydrones[6], indicate that the long-wavelength absorption is to be assigned to a CT-transition from a less polar ground state to a more polar excited state. On the other hand, the 'Wurster's Blue' radical cation derived from 4,7-bis(dimethylamino)[2.2]paracyclophane, which has been synthesized for comparison[7], shows absorptions in the same wavelength region [$\lambda_{max} = 585$ nm, in 1,2-dichloroethane]. Hence, on the basis of the absorption spectra alone an unambiguous distinction between (1)/(2) and the corresponding zwitterions (1a)/(2a) is rather difficult. ESR measurements on (1) and (2) in the solid state and on (2) in solution in 1,2-dimethoxyethane between 20 and 70°C[8], as well as the regular line-width of the ^{1}H-NMR absorptions of (1) and (2), exclude *para*magnetic ground states of zwitterionic structures. The problem of the existence and electronic structure of cyclophane-zwitterions of the type (1a) and (2a) needs, however, further investigation including the synthesis of TMPD-[2.2]paracyclophanes with stronger acceptors than *p*-benzoquinone.

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(1), 66212-55-3; (2), 66183-93-5; (3), 66212-59-7; (4), 66183-99-1; (5), 66212-58-6; (6), 66183-98-0; (7), 66212-57-5; (8), 66183-97-9; (9), 66212-56-4; (10), 66183-96-8; (11), 66289-65-4; (12), 66183-95-7; *p*-benzoquinone, 106-51-4; TMPD, 100-22-1

[1] Orientation Dependence of Charge-Transfer Interactions, 16th Communication.—15th Communication: *H. A. Staab, H.-E. Henke*, Tetrahedron Lett. (in press).

[2] For further references see *H. A. Staab, U. Zapf, A. Gurke*, Angew. Chem. *89*, 841 (1977); Angew. Chem. Int. Ed. Engl. *16*, 801 (1977).

[3] Cf. the partly contradictory statements of *H. Kainer, D. Bijl, A. C. Rose-Innes*, Naturwissenschaften *41*, 303 (1954); *D. Bijl, H. Kainer, A. C. Rose-Innes*, J. Chem. Phys. *30*, 765 (1959); *Y. Matsunaga, C. A. McDowell*, Nature (London) *185*, 916 (1960); *M. E. Browne, A. Ottenberg, R. L. Brandon*, J. Chem. Phys. *41*, 3265 (1964); *G. T. Pott, J. Kommandeur*, Mol. Phys. *13*, 373 (1967).

[4] Element analyses and spectroscopic data are in agreement with the structures mentioned.

[5] Cf. *H. J. Reich, D. J. Cram*, J. Am. Chem. Soc. *91*, 3534 (1969); *H. A. Staab, W. Rebafka*, Chem. Ber. *110*, 3333 (1977); *H. A. Staab, H. Haffner, ibid. 110*, 3358 (1977).

[6] *W. Rebafka, H. A. Staab*, Angew. Chem. *85*, 831 (1973); *86*, 234 (1974); Angew. Chem. Int. Ed. Engl. *12*, 776 (1973); *13*, 203 (1974); *H. A. Staab, W. Rebafka*, Chem. Ber. *110*, 3333 (1977); *H. A. Staab, C. P. Herz, H.-E. Henke, ibid. 110*, 3351 (1977); *H. A. Staab, C. P. Herz*, Angew. Chem. *89*, 839 (1977); Angew. Chem. Int. Ed. Engl. *16*, 799 (1977).

[7] Starting from 4-amino[2.2]paracyclophane *via* the 4-acetylamino-, 4-acetylamino-7-nitro- and 4-amino-7-nitro[2.2]paracyclophanes, 4,7-diamino[2.2]paracyclophane was obtained which was methylated to the 4,7-bis(dimethylamino) compound (*R. Reimann*, Diplomarbeit, Universität Heidelberg 1976).

[8] We thank *H. Zimmermann*, Department of Molecular Physics, for the ESR measurements and Dr. *H. Weger* for preliminary investigations.

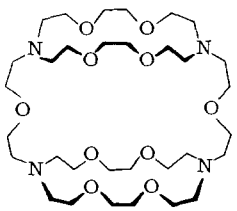
ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

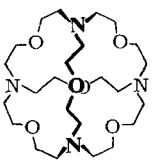
The influence of metals on heme biosynthesis and heme metabolism are examined by *T. R. Tephly, G. Wagner, R. Sedman,* and *W. Piper*. Investigation of the effects on the enzymes of heme biosynthesis has provided information about the regulation of this metabolic pathway and about the toxicology of various metals. Therapeutic advances can be expected in the fields of metal poisoning and hereditary disorders of heme biosynthesis. [Effects of Metals on Heme Biosynthesis and Metabolism. Fed. Proc. *37*, 35—39 (1978); 39 references]

[Rd 9 IE]

The chemistry of macrocyclic inclusion complexes—cryptates—is the topic of a review by *J.-M. Lehn*. The ligands (cryptands) characteristically have three-dimensional cavities which can take up, *e.g.*, alkali and alkaline earth metals. Cylindrical macrotricyclic compounds such as *(1)* are known to



(1)

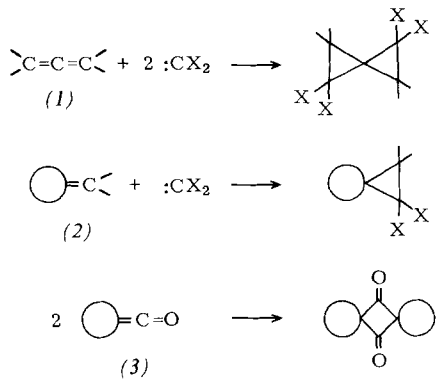


(2)

form complexes with one or two metal ions, *e.g.* Na^+; in the 1:1 complexes the cation appears to be preferentially located in one of the rings or on one side of the cavity. Spherical macrotricyclic compounds such as *(2)* form very stable complexes with alkali metal ions and the ammonium ion. Diprotonated *(2)* contains a H-bonded H_2O molecule in the cavity; tetraprotonated *(2)* can take up a halide ion. [Cryptates: The Chemistry of Macropolycyclic Inclusion Complexes. Acc. Chem. Res. *11*, 49—57 (1978); 82 references]

[Rd 16 IE]

Syntheses of carbocyclic spiro compounds by cycloaddition are surveyed by *A. P. Krapcho*. Examples are additions of carbenes to allenes *(1)* and (substituted) methylenecycloalkanes *(2)*. Spiro compounds are also accessible by cyclodimerization



(1)

(2)

(3)

of cyclic ketenes *(3)* or by Diels-Alder reaction of (substituted) methylenecycloalkanes and dienes. [Synthesis of Carbocyclic Spiro Compounds *via* Cycloaddition Routes. Synthesis *1978*, 77—126; 492 references]

[Rd 14 IE]

Annual surveys of work published in 1976 are presented in a volume of Journal of Organometallic Chemistry. No less than 432 pages are devoted to the organic compounds of the following elements: zinc, cadmium, boron, aluminum, gallium, indium, thallium, antimony, bismuth, manganese, technetium, rhenium, nickel, palladium, and platinum; ferrocene derivatives are also considered. [J. Organomet. Chem. *147* (1978); numerous references for each article]

[Rd 15 IE]

BOOK REVIEWS

Methodische Fortschritte im medizinischen Laboratorium. Band 4: Diagnostik hämorrhagischer Diathesen (Methodological Advances in Medical Laboratories. Vol. 4: Diagnosis of Hemorrhagic Diatheses). Edited by *A. Englhardt* and *H. Lommel* together with *L. Róka* and *W. G. A. Ohler*. Verlag Chemie, Weinheim—New York 1977, 1st Edit., 203 pp., bound, DM 58.—.

The growing importance of blood-clotting disorders in various diseases and the continuing progress in the therapeutic treatment of the blood-coagulation system make it universally essential to have up-to-date information on the physiology and pathophysiology of coagulation and on the procedures available for its physiological investigation. The editors have succeeded in conscripting a group of experts for this book. The work contains seven chapters: 1) Principles of hemostasis and analytical coagulation diagnostics; 2) Formulation of indications for the analysis of hemostasis; 3) Hereditary and acquired coagulopathies; 4) Thrombocytic coagulation disorders; 5) Anticoagulation; 6) Quality control in physiological methods of investigating coagulation; and 7) Coagulation

diagnostics with chromogenic peptide substrates. An Appendix (p. 190) names suppliers of reagents and automatic equipment for coagulation analysis.

The book can be recommended without hesitation. It will assuredly soon find its place in reference libraries of even the smaller medical departments, in appropriate clinics, and in intensive-care units. Hospital doctors, anesthetists, surgeons, and clinical chemists concerned with the diagnosis and treatment of hemorrhagic diatheses will all use this book with advantage.

Friedrich Willig [NB 414 IE]

Metal Ions in Biological Systems. Vol. 6: Biological Action of Metal Ions. Edited by *H. Siegel*. Marcel Dekker, Inc., New York—Basel 1976. xiii, 453 pp., numerous figs., bound, Sfr. 130.—.

Under the title "Biological Action of Metal Ions" are collected aspects as diverse as the participation of metal ions in enzyme catalysis, the occurrence of vanadium in animate nature, and the effects of Ca^{2+} on regulation of muscle activity.

In Chapter 1 *J. Chlebowski* and *J. E. Coleman* discuss the function of zinc in zinc metalloenzymes. A clear and stringent definition of the term "zinc metalloenzymes" enables the authors to concentrate the discussion on a few well studied enzymes (carboxypeptidase A and B, thermolysin, alkaline phosphatase, carboanhydrase, superoxide-dismutase, alcoholdehydrogenase, aldolase, aspartate-transcarboxylase, transcarboxylase, and DNA-polymerase). This special section is preceded by a very good discussion of the techniques for investigating metalloenzymes by all the modern physicochemical methods applicable in this field, *e.g.* absorption, CD, ESR, and NMR spectroscopy. Anyone interested in metalloenzymes can draw stimulation from this section in particular. The literature is cited up to 1973 and is continued by a section "Recent Developments" up to 1976.

Chapter 2 *(W. R. Biggs* and *J. H. Swinehart)* deals with the occurrence of vanadium in plants and animals. Because of the general ignorance of the function of this metal ion in biochemistry, pride of place is given to the consideration of the vanadium content of plants and animals. Correspondingly, further sections are concerned, for example, with the uptake and uptake processes, mainly by comparison of different species, and they give no clues on the molecular level. The most recent references are from 1973.

Chapter 3, by *P. W. Schneider*, is devoted to the chemistry of nitrogen fixation. This extremely clear and precisely written review shows the present state of knowledge in the field of the molybdenum and iron proteins that are present in nitrogenase. Comparison with the inorganic-organic complexes of the transition metals leads to a far-reaching discussion of the nitrogen-reduction mechanism. Here too references are up to 1973.

Chapter 4 *(D. W. Darnall* and *E. R. Birnbaum)* deals with the stabilizing influence of calcium on the conversion of trypsinogen into trypsin. As both the primary sequence and the spatial structure of trypsin and trypsinogen are known, statements can be made on a molecular plane about the effect of calcium on this process, although no generalizations are permissible. References are dated up to 1973 and taken up to 1975 by an addendum.

In Chapter 5, *K. S. Rajan, R. W. Colburn,* and *J. M. Davis* describe the participation of metal chelates in the accumulation and transport of neurotransmitters. Much space is given to the hypothesis that ternary complexes of ATP-metal ion and neurotransmitters (amines) constitutes the basis for the transport of these biologically active amines through the lipid matrix. Since it is now certain that proteins take part in many transport processes, any theory postulating transport through biological membranes solely by chelate formation seems unlikely. Here too the references are supplemented by an addendum up to 1976.

In the last Chapter *F. N. Briggs* and *R. J. Salora* make an attempt to give a comprehensive review of the role of calcium in regulation of muscle contraction. It is indeed tempting to treat the role of calcium in terms of electromechanical coupling, regulation of actomyosin-ATPase, and regulation of the calcium-transport ATPase in a single review article, yet the authors must leave a few gaps. For example, new developments in the phosphorylation of troponin are not considered, although they have been known since 1974 and 1975 *inter alia* from *Perry*'s school. Similar remarks apply to the phosphorylation of myosin. The older literature, in particular, is reviewed in detail (347 references up to 1973).

The heterogeneity of the article makes it clear that "bioinorganic chemistry" cannot be regarded as an independent branch of science, as the editors claim in the Foreword.

Ludwig Heilmeyer [NB 417 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Analytical Applications of NMR. By *D. E. Leyden* and *R. H. Cox*. Vol. 48 of the series "Chemical Analysis. A Series of Monographs on Analytical Chemistry and its Applications". Edited by *P. J. Elving, J. D. Winefordner*, and *I. M. Kolthoff*. John Wiley & Sons, New York 1977. ix, 456 pp., bound, $ 20.75.—ISBN 471-53403-X

Organic Compounds of Sulphur, Selenium, and Tellurium, Vol. 4. Senior Reporter: *D. R. Hogg*. The Chemical Society, London 1977. xxii, 527 pp., bound, DM 178.50.—ISBN 0-85186-289-6—A volume of the series "Specialist Periodical Reports"

Synthesis of Prostaglandins. By *C. S. Szantay* and *L. Novak*. Publishing house of the Hungarian Academy of Sciences, Budapest 1978. viii, 267 pp., bound DM 36.80.— ISBN 963-05-1303-X

Batteries, Vol. 2: Lead-Acid Batteries and Electric Vehicles. Edited by *K. V. Kordesch*. Marcel Dekker, New York 1977. xiii, 514 pp., bound SFrs. 188.—.—ISBN 0-8247-6489-7

Heterocyclic Chemistry. By *J. A. Joule* and *G. F. Smith*. Van Nostrand Reinhold, Wokingham 1978. viii, 378 pp., bound £ 12.00. — ISBN 0-442-30211-8

Non-Isothermal Reaction Analysis. Edited by *E. Koch*. Academic Press, London 1977. xx, 607 pp., £ 32.50.—ISBN 0-12-417350-0

Electron Spin Resonance, Vol. 4. Senior Reporter: *P. B. Ayscough*. The Chemical Society, London 1977. ix, 302 pp., bound £ 24.00.—ISBN 0-85186-781-2.—A volume in the series "Specialist Periodical Reports".

Proceedings in Life Sciences. New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity. Edited by *H. Wagner* and *P. Wolff*. Springer-Verlag, Berlin 1977. xi, 286 pp., bound DM 67.—.—ISBN 3-540-08292-1

Instrumental Organic Elemental Analysis. Edited by *R. Belcher*. Academic Press, London 1977. xi, 299 pp., bound £ 14.00. —ISBN 0-12-085950-5

Principles of Colloid and Surface Chemistry (Undergraduate Chemistry: A Series of Textbooks, Vol. 4). By *P. Hiemenz*. Marcel Dekker, New York 1977. xi, 516 pp., bound SFrs. 64.—.—ISBN 0-8247-6573-7

Topological Approach to the Chemistry of Conjugated Molecules. By *G. Graovac, I. Gutman* and *N. Trinajstić*. Vol. 4 of the series „Lecture Notes in Chemistry". Edited by *G. Berthier, M. J. S. Dewar, H. Fischer, K. Fukui, H. Hartmann, H. H. Jaffé, J. Jortner, W. Kutzelnigg, K. Ruedenberg, E. Scrocco*, and *W. Zeil*. Springer-Verlag, Berlin 1977. vii, 123 pp., sewed DM 18.—.—ISBN 3-540-08431-2

Ullmanns Encyklopädie der technischen Chemie. Edited by *E. Bartholomé, E. Biekert, H. Hellmann, H. Ley* (decreased), and *W. M. Weigert* (decreased). Verlag Chemie, Weinheim 1977. 4th revised and enlarged edition.
Vol. 13: Hormone bis Keramik, xv, 735 pp., bound DM 430.—.—ISBN 3-527-20013-4
Vol. 14: Keramische Farben bis Kork. xv, 717 pp., bound DM 430.—.—ISBN 3-527-20014-2

Organische Chemie. By *K. Freudenberg* and *H. Plieninger*. Quelle & Meyer, Heidelberg 1977. 13th completely revised edition. 301 pp., sewed DM 19.80.—ISBN 3-494-02069-8

Contemporary Topics in Polymer Science, Vol. 2. Edited by *E. M. Pearce* and *J. R. Schaefgen*. Plenum Press, New York 1977. vii, 316 pp., bound $ 39.00.—ISBN 0-306-36262-7

Bericht über die 28. Getreidechemiker-Tagung. Granum-Verlag, Detmold 1977. 210 pp., sewed DM. 30.—.

Characterization of Solutes in Nonaqueous Solvents. Edited by *G. Mamantov*. Plenum Press, New York 1978. vii, 325 pp., bound $ 42.00.—ISBN 0-306-31108-9

Aspects of Homogeneous Catalysis. A Series of Advances, Vol. 3. Edited by *R. Ugo*. D. Reidel Publishing Co., Dordrecht 1977. viii, 240 pp., bound $ 39.50.—ISBN 90-277-0786-3

Pollution Evaluation: The Quantitative Aspects (Environmental Science and Technology Series, Vol. 2). By *W. F. Pickering*. Marcel Dekker, New York 1977. v, 199 pp., bound SFrs. 54.—.—ISBN 0-8247-6621-0

Phosphorus. An Outline of its Chemistry, Biochemistry and Technology. By *D. E. C. Corbridge*. Elsevier Scientific Publishing Co., Amsterdam 1978. x, 455 pp., bound $ 59.60.—ISBN 0-444-41661-7

Further Perspectives in Organic Chemistry. Ciba Foundation Symposium 53 (New Series). Excerpta Medica, Amsterdam 178. viii, 212 pp., bound $ 19.75.—ISBN 0-444-90001-2

Inorganic and Nutritional Aspects of Cancer. Edited by *G. N. Schrauzer*. Plenum Press, New York 1978. xi, 351 pp., bound $ 39.00.—ISBN 0-306-32691-4

Rodd's Chemistry of Carbon Compounds, Vol. 3, Part G. Edited by *S. Coffey*. Elsevier Scientific Publishing Co., Amsterdam 1978. 2nd Edit. xviii, 343 pp., bound $ 69.75.—ISBN 0-444-41573-4

Fundamental Research in Homogeneous Catalysis. Edited by *R. Ugo* and *M. Tsutsui*. Plenum Press, New York 1977. x, 242 pp., bound $ 33.00.—ISBN 0-306-34441-6

Critical Stability Constants. Vol. 3: Other Organic Ligands. By *A. E. Martell* and *R. M. Smith*. Plenum Press, New York 1977. xvi, 495 pp., bound $ 59.40.—ISBN 0-306-35213-3

Computers in Chemical Education and Research. Edited by *E. V. Ludena, N. H. Sabelli*, and *A. C. Wahl*. Plenum Press, New York 1977. xi, 476 pp., bound $ 45.00.—ISBN 0-306-31071-6

Biochemie und Physiologie der Phytoeffektoren. By *H. Gräser*. Verlag Chemie, Weinheim 1977. 446 pp., bound DM 128.—. —ISBN 3-527-25748-9

Lehrbuch der Kolloidwissenschaft. By *H. Sonntag*. VEB Deutscher Verlag der Wissenschaften, Berlin 1977. 325 pp., bound *ca.* DM 43.—.

Dielectric and Related Molecular Processes, Vol. 3. Senior Reporter: *M. Davies*. The Chemical Society, London 1977. ix, 259 pp., £ 23.00.—ISBN 0-85186-525-9.—A volume in the series "Specialist Periodical Reports"

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What Do We Know about the Metal-Metal Bond?

By Heinrich Vahrenkamp[*]

Dedicated to Professor Heinrich Nöth on the occasion of his 50th birthday

Almost all main group and subgroup metals are able to form metal-metal bonds. The bond order ranges from weak interaction to a quadruple bond, and the degree of aggregation from a dinuclear entity to a three-dimensional network. In spite of numerous physicochemical studies, not all aspects of the metal-metal bond are understood. The ability of metal-metal linked polynuclear complexes to serve as a reservoir for missing or excess electrons enables them to react both with nucleophilic or reducing reagents and with electrophilic or oxidizing reagents. The intermediate position occupied by clusters between simple complexes and the bulk metal is of theoretical and practical significance.

1. Introduction

Two extreme answers can be given to the question posed in the title. One is: So much that compounds containing metal-metal bonds have already been treated in about 70 reviews and monographs cited in this article[1–62]. The other answer is: So little that the significance of metal-metal interactions is still uncertain even in the simplest compounds, as is illustrated by the fact that the Cs—Cs distances in cesium fluoride are 20% shorter than in cesium metal[63] and that careful analysis of X-ray measurements on the complex $[Fe(CO)_2C_5H_5]_2$ showed there to be zero electron density midway between the two iron atoms[64]. Both answers prompted the author to write this article and to give it the chosen title.

The development of the chemistry of metal-metal bonds is intimately connected with X-ray crystal structure analysis. The availability of large scale computers and automatic diffractometers led to a breakthrough in both fields during the past decade. Even the concept of a "metal-metal bond" could only become popular some 20 years ago, once some crystal structure analyses had demonstrated its existence in solid-state and molecular compounds[65–69] for which rather adventurous structural proposals had only recently been voiced[70, 71]. Finally, the use of Fourier series for determining atomic positions in crystals was first demonstrated for Hg_2Cl_2 50 years ago, the metal-metal bond of which was then viewed merely as a curiosity[72].

We now know that almost all metallic elements participate in metal-metal bonding and that d elements are particularly good at doing so. The bond orders range from very weak interaction, such as in $Cr_2Cl_9^{3-}$[73] to the quadruple bond, as in $Cr_2(\eta\text{-}C_3H_5)_4$[74]. The estimated and experimental bond energies cover the range between almost 0 (monomer-dimer equilibrium[42]) to over 300 kcal/mol[75]. Complete transition from the metallic state to isolated mononuclear complexes or metal ions has been accomplished in compounds with more or less extended metal-metal linkages. The metal-metal bond has indeed become "textbook chemistry"[76]; however, there are many aspects yet to be elucidated.

The sheer volume of available material precludes a description of all compounds containing metal-metal bonds. The last attempt to do so for the transition metals dates from 1967[5], and the last attempt to cover all transition metal clusters was made in 1971[32]. In this present article, an attempt

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Chemisches Laboratorium der Universität
Albertstrasse 21, D-7800 Freiburg (Germany)

is made to highlight points of a general nature and to examine aspects of systematics, structure, and bonding as well as reactivity and applicability of compounds with metal-metal bonds. The examples are selected with the aim of providing the best possible entry to the extensive literature.

2. Classification

The lightest metal lithium (in $[LiCH_3]_4$[77]) and the heaviest natural metal uranium (in $U_6O_4(OH)_4(SO_4)_6$[31]) undergo metal-metal interactions. The number of compounds with metal-metal bonds formed by the metals lying between these two extremes varies; a maximum occurs in the middle of the transition metal series, and that is where the main emphasis of this article lies. The early main group metals[78] and the lanthanoids[79,80] form a few compounds of this type, while the post-transition elements[13,81] form many; combination with transition metals[6,12] provides a means of forming stable metal-metal bonds for all metallic elements.

The conditions for the occurrence of metal-metal bonds have often been discussed[5,14,31,32,47,51]. The conclusions reached comply with chemical experience, but are only qualitative and do not necessarily follow from theoretical considerations. The situation is clearest in the large number of polynuclear complexes in which the tendency to achieve an 18-electron configuration is met by covalent bonding with other metal atoms. In many other cases, the metal-metal bond is a compromise adopted in the absence of other bonding partners. Examples are the electron-deficient compounds[78], the lower halides of Nb, Ta, Mo, W, and Re[19,31,34,62], and the metallocenes of the early transition metals[82,83]. However, structural constraints can also give rise to metal-metal bonds. Thus the crystal lattice of the bonding partners in many solids imposes spatial proximity of metal atoms[20,51,59,84,85], and the geometrical requirements of bridging ligands can lead to the contact of two metal atoms[18,23,26]. It is immaterial whether two identical or two different metal atoms interact with each other.

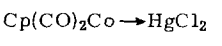
2.1. Units Containing Two Metal Atoms

Most of the compounds considered contain two linked metal atoms[1-62]. All kinds of metal-metal interaction are encountered in dinuclear compounds, with bridging ligands frequently contributing to the stabilization of unusual kinds of bonding and bond orders.

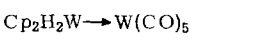
2.1.1. Single Bonds

In organometallic compounds, any two molecular fragments which each need one electron to complete the inert gas configuration will generally be able to combine. The product is usually a dinuclear compound with a metal-metal single bond involving main group and/or subgroup elements. An analogous rule can be formulated for solid state chemistry which states that transition metal ions with d^1 configuration can approach pairwise in the crystalline network. However, this rule is not always obeyed and M_2 units with a single bond are also encountered among other d-electron configurations.

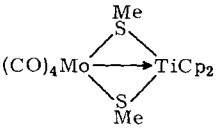
In addition to the large number of systems which can be described in this way, there are others requiring formulation with donor-acceptor metal-metal bonds[86-88]. Unequivocal cases are, *e.g.*, *(1)*[89] and *(2)*[90]; and *(3)*[91] and *(4)*[92] are also best formulated in these terms.



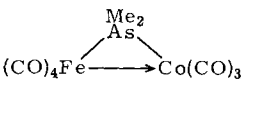
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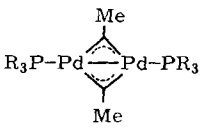


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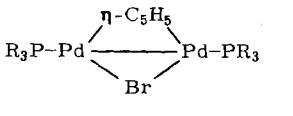


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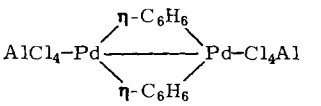
The metal-metal single bond in complexes can be bridged by up to four ligands; in solids it can "reach through" between a maximum of four anions in the lattice. The commonest examples are the linkage of ML_6 octahedra *via* shared edges (two bridging atoms) or *via* shared faces (three bridging atoms)[17,22,26,51]. Even ligands normally occupying terminal positions can act as bridges in dinuclear complexes. Examples are the allyl ligand in *(5)*[93], the cyclopentadienyl ligand in *(6)*[94], benzene in *(7)*[95], and the cycloheptatrienyl ligand in *(8)*[96]. Numerous unusual organic double bond systems likewise owe their existence to stabilization in a dinuclear complex[46].



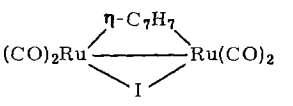
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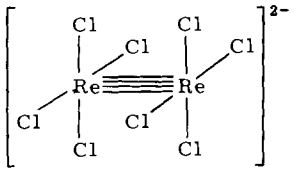
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2.1.2. Multiple Bonds

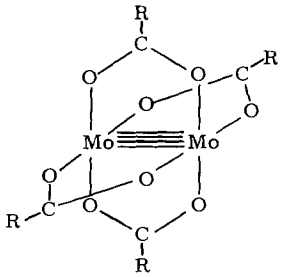
Bond orders of 2, 3, and 4 between metal atoms are no longer unusual. Examples are encountered most frequently in units containing two metal atoms. While the chloro complexes and acetates of some heavy transition metals were the first to exhibit metal-metal multiple bonds[15,16], the phenomenon has meanwhile been observed for most transition metals and classes of compounds.

The elements showing the greatest tendency to form multiple bonds are chromium, molybdenum, tungsten, and rhenium. Apart from the meanwhile classical compounds *(9)*—*(11)*[14] and their derivatives[15,16], there are numerous other similar units of stoichiometry M_2X_8 (quadruple bond) and M_2X_6 (triple bond). X may stand for alkyl[97], allyl[74], dialkylamino[98], alkoxy[99], and halogen[100].

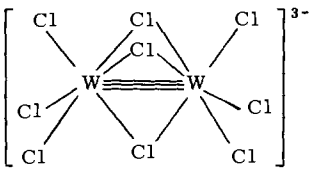
While metal-metal multiple bonds are rare in solid state chemistry[5,51,59], a large number of organometallic complexes with such bonds have recently been found. A condition for the stability of these compounds is that the M_2 unit



(9)

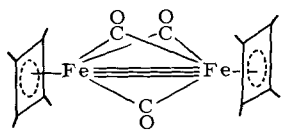


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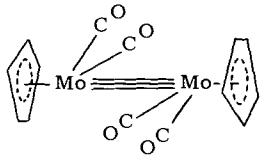


(11)

be protected by numerous or bulky ligands, as demonstrated particularly well by pentamethylcyclopentadienyl complexes[33]. Compounds *(12)*[101] and *(13)*[102] are two typical examples.

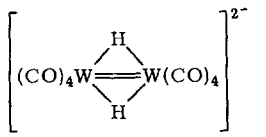


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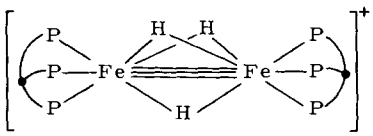


(13)

The necessary crowding in the ligand sphere also explains why bridging H atoms having very modest spatial requirements go so well with metal-metal multiple bonds; up to four such bridges may occur[103]. Double and triple bonds are observed [cf. *(14)*[104] and *(15)*[105], respectively]. A valid alternative to the double bond formulation in *(14)* is a formulation analogous to diborane with two WHW three-center bonds.

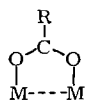


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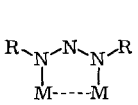


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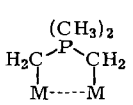
Bidentate ligands with three atoms in the bridge are able to force two metal atoms relatively close together. As a result, metal-metal multiple bonds are favored in carboxylates[5, 16, 18], triazenides[106], and derivatives of trimethyl(methylene)phosphorane[107] [cf. *(16)*—*(18)*]. In compounds of Cu[I][108], Ag[I][109], and Au[I][110] this leads to some degree of ambiguity because they can also be formulated without metal-metal bonds on the basis of their electronic structure, although the metal-metal distances are very short in some cases.



(16)



(17)



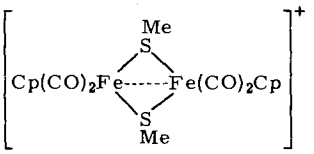
(18)

2.1.3. Weak Interactions

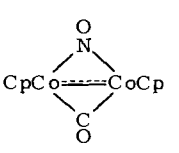
In many solids displaying a tendency to undergo metal-metal bonding, the attractive forces between the metal atoms are insufficient to displace them significantly from the centroids of their anion polyhedra. The result of this balance of forces is the weak metal-metal interaction in numerous compounds of stoichiometry $MHal_2$, MO_2, MOHal, and $M'_3(M_2Hal_9)$[5, 51, 59]. The structures and magnetic moments of such compounds indicate M_2 units with metal-metal bond orders of zero to two, depending upon the metal, anion, and stoichiometry. The usual relation between electronic structure and bond order is invalidated by stereochemical factors in these compounds.

This phenomenon is hardly encountered in organometallic complexes. Although the metal-metal distances can admittedly be varied between wide limits by the influence of bridging ligands (see Section 3.1), uncoupling of the two metal atoms, and hence paramagnetism given an even number of electrons, is only seldom observed[5, 17]. In contrast, inorganic dinuclear complexes with chalcogen and halogen bridges display a highly varied magnetochemistry which can be rationalized in part by weak metal-metal interactions[23, 26, 35]. In particular, the chemistry of Cu[II][7, 25] and Cu[III][18, 29] is rich in structural and magnetic anomalies.

Still anomalous and yet unequivocally definable are the half-integral bond orders found in some organometallic dinuclear complexes. There are one or three electrons too few for both metal atoms to achieve an 18-electron configuration. Such complexes are formed on use of ligands with an uneven number of electrons or by redox reactions. Complexes



(19)



(20)

(19)[111] and *(20)*[112, 113] having metal-metal bond orders of one-half and one-and-a-half, respectively, represent these rather atypical compounds.

2.2. Aggregates

The commonest form of aggregated systems containing several linked metal atoms are clusters; however, individual metal-metal bonds or several of them may also occur in chains, rings, and cage-like structures. It cannot usually be predicted whether aggregates or simple systems with metal-metal multiple bonds will be formed. The number of bonding partners seems to be an important criterion (see Section 2.1.2). Large numbers of ligands or anions favor multiple bonding, small numbers promote aggregation.

2.2.1. Short Chains of Metal Atoms

Arrangement of a few transition metal atoms in a short chain is relatively uncommon. It is hardly observed in solid-state compounds and inorganic complexes; only organometallic chemistry provides a few isolated examples. The simplest

cases are linear homoatomic systems such as *(21)*[114] or L_nMX_2 derivatives such as *(22)*[115].

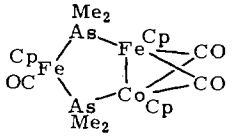
$[(CO)_5Mn—Mn(CO)_4—Mn(CO)_5]^-$ *(21)* $(CO)_5Mn—Pd(py)_2—Mn(CO)_5$ *(22)*

Under suitable electronic conditions bent structures also occur[116,117], leading almost as far as arrangement of the metal atoms in an equilateral triangle[118]. Unusual bridging ligands[119] and donor-acceptor metal-metal bonds[120] are also found in these trinuclear complexes. The chain arrangement of four transition metal atoms has so far only been described for complex *(23)*[121], which is probably only a short-lived intermediate[122].

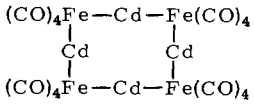
$Cl—Os(CO)_4—Os(CO)_4—Os(CO)_4—Au—PPh_3$ *(23)*

2.2.2. Rings and Cages

Linkage of two transition metal atoms *via* a chelate ligand to form a ring system is very common [cf. *(16)—(18)*]. Three and four metal atoms are joined together in rings containing four to eight members. Compounds *(24)*[123] and *(25)*[124] are typical examples. The structural chemistry of rings containing four metal atoms is of great variety; all



(24)



(25)

possibilities between zero and four metal-metal bonds are represented[10].

Numerous cage-like polynuclear complexes combine the bonding tendencies of the main group elements (as bridging ligands) and the transition metals (as polynuclear complex units). This relation is seen most clearly in polynuclear sulfur complexes[55]; however, other combinations of main group elements and transition metals also exhibit the full range of possibilities, from the pure cage structure without metal-metal interaction to the complete aggregation of metal atoms to form clusters. Polynuclear complexes with four metal atoms[17,125-127] provide the clearest illustrations.

The relationship between the bonding in polyhedral boranes and transition metal clusters[58] explains why structural units of these two classes of substances can be combined together. Incorporation of M_2, M_3, and M_4 units into the cage structure of boranes and carboranes[128] is accordingly a rapidly developing area of chemistry. The structures of two such cages are shown in order to demonstrate the scope of such reactions (Fig. 1).

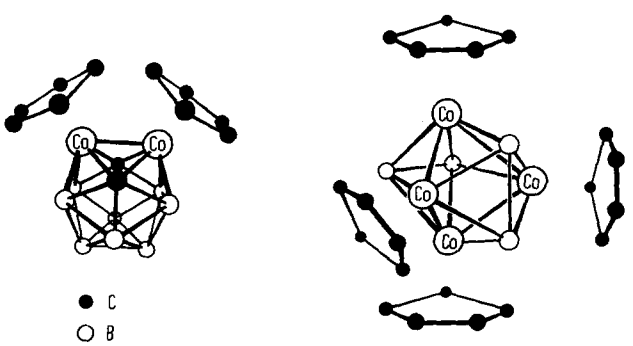


Fig. 1. Structures of $(CpCo)_2C_2B_8H_{10}$ [128] (left) and $(CpCo)_4B_4H_4$ [129] (right).

2.2.3. Clusters

Clusters of main group[13] and transition metals[10,11,28,56] have recently been reviewed and details are therefore readily available. The enormous structural variety of clusters still frequently resists systematization. The principal general points to be noted are: in addition to the well known arrangements of metal atoms as triangles, tetrahedra, and octahedra, many other geometries occur; clusters comprising up to 18 metal atoms have been found whose coordination resembles that in the bulk metal; clusters occur in solids and in inorganic and organometallic complexes; and the number of electrons and bond orders in clusters can deviate appreciably from the values expected by simple rules. Clusters provide the clearest demonstration that aggregates of several metal atoms are only partly governed by the rules discovered in the study of units containing two metal atoms, and that in some respects they already exhibit the cooperative phenomena of extended metal atom arrangements.

2.3. Extended Arrangements

In the region between metallic and ionic bonding and between metallic and covalent bonding we find compounds with infinitely extended arrangements of metal atoms. These compounds can be classified as "dilute metals" with the metal atoms linked in a kind of three-dimensional network, "two-dimensional metals" with layer-type linkage, and "one-dimensional metals" with chain-like linkage of the metal atoms. Practical interest in the optical and electrical properties of such compounds has greatly stimulated their study in recent years.

2.3.1. Chain Structures

The chain structures include the only extended metal atom arrangements that can still be described by means of covalent metal-metal bonds. These are stoichiometrically pure, square-planar d^8 complexes which are stacked with short metal-metal bonds in their crystals. They include $[Ir(CO)_3Cl]_x$[130] and similar iridium compounds[131] in which each iridium atom achieves an 18-electron configuration by two metal-metal bonds.

Normally, however, d^8 complexes crystallize without pronounced metal-metal interaction[36,43]; only partial oxidation leads to mutual approach of the metal atoms, especially in the platinum complexes, with all its drastic physical consequences which can only be described in terms of a band model[36,44,54,132]. Optical, electrical, magnetic, and structural properties attributable to a one-dimensional infinite linkage of metal atoms are also found for polymeric ligand-bridged complexes, for crystalline $A^+MX_3^-$ compounds, and for some metal trihalides[24,30]. Finally, many Zintl phases[133] and transition metal sulfides[85] and phosphides[84] have long been known to contain chains of metal atoms in their crystals.

2.3.2. Layers and Three-Dimensional Networks

Numerous metal sulfides, selenides, phosphides, and arsenides have metallic properties because the modest electron affinity of the heavy chalcogen and pentel[*] atoms permit electron delocalization, *i.e.* metallic interaction. The structures of these compounds frequently indicate extended metal atom linkages[84, 85, 133]. Two- and three-dimensional metal-metal interactions are also being increasingly observed in halides and oxides of metals in formally low oxidation states[24, 59]. A classical example of metal atom layers is Ag_2F[59], and a recent one is found in the lanthanoid monochlorides[80]. Sc_7Cl_{10}[79] represents a transition between two-dimensional and three-dimensional linkage. And the alkali metal suboxides Rb_6O and Cs_7O[134] are excellent examples of "dilute metals", with ionic regions embedded in a metallic network.

As the extension of metal-metal interactions increases, the resemblance to metals becomes closer and closer. This also means that statements concerning electron balance and bond order become meaningless once the basic premises of localizable and covalent bonds no longer apply.

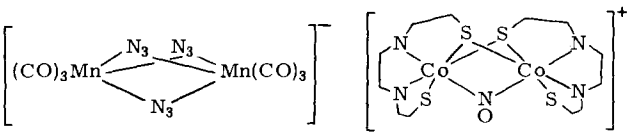
3. Studies on the Nature of the Bond

Classical experimental data in the chemistry of metal-metal bonds are interatomic distances and magnetism. However, these data do not always permit unequivocal delineation, and they do not adequately account for energetic information. In spite of the complicated nature of most of these compounds, the significance of other experimental and calculation methods of chemistry is therefore increasing in this field too. They are still mainly limited to units containing two metal atoms.

3.1. Bond Lengths

It is generally agreed that metal-metal bonds should be considered when the metal atom distances are of the same order as in the metal. The variability of metal-metal distances *(vide infra)*, however, precludes any definition of covalent metal atom radii and conclusions based solely on bond lengths. For instance, the metal-metal distances in complexes *(26)*[135] and *(27)*[136], for which the 18-electron rule predicts *no* metal-metal bonding, are shorter than in complexes *(28)*[69] and *(29)*[137] of the same metals *with* metal-metal bonding. Contradictions of this kind are encountered above all in the chemistry of univalent copper[7, 25].

The metal-metal bond defines a relatively flat energy minimum as a function of the interatomic distance. This fact is just as apparent in the structures of polynuclear complexes as in the flexibility of many bulk metals and the fluctuation of the metal atoms in individual clusters[138]. For this reason, the identification of a metal-metal bond requires the comparative study of two compounds of similar stereochemistry. The drastic change in geometry on going from *(30) without* metal-metal bonding to *(31) with* metal-metal bonding constitutes proof of the structure-determining power of this bond[139].



(26), Mn–Mn = 2.89 Å

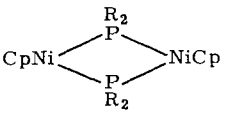
$(CO)_5Mn$–$Mn(CO)_5$

(28), Mn–Mn = 2.93 Å

(27), Co–Co = 2.77 Å

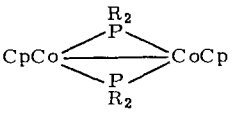
$[(CN)_5Co$–$Co(CN)_5]^{6-}$

(29), Co–Co = 2.80 Å



(30), Ni–Ni = 3.36 Å

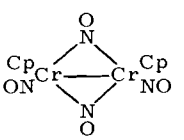
R = C_6H_5



(31), Co–Co = 2.56 Å

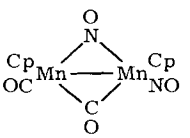
R = C_6H_5

Variability of the metal-metal bond lengths is especially clear in complexes with bridging ligands which keep the metal atoms together even in cases of weak interaction. Thus the Fe—Fe distances in bridged dinuclear complexes having an Fe—Fe bond lie between 2.37 and 3.05 Å[17], and the influence of bridging atom radii and the number of ligands on the metal-metal distances can be followed systematically[17, 140]. On the other hand, the complexes *(32)*—*(34)*[141] in which the bond lengths do not differ significantly show the stereochemistry of the ligand system to exert a greater influence on these bond lengths than the differing radii of the metal atoms.



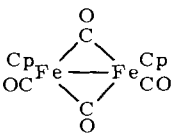
(32)

Cr–Cr = 2.61 Å



(33)

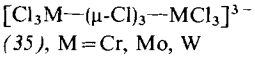
Mn–Mn = 2.57 Å



(34)

Fe–Fe = 2.53 Å

In cases of strong metal-metal interactions (*i.e.* generally with heavy transition metals) a compromise is often observed between the steric requirements of the coordination partners and mutual attraction of the metal atoms. Complexes *(35)*[73] and *(36)*[142] demonstrate how the bond between the metal atoms increases with increasing atomic weight. The optimum short metal-metal distance is achieved in none of these cases and one therefore speaks of "submaximum overlap".

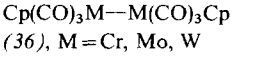


(35), M = Cr, Mo, W

Cr—Cr = 3.12 Å

Mo—Mo = 2.66 Å

W—W = 2.41 Å



(36), M = Cr, Mo, W

Cr—Cr = 3.28 Å

Mo—Mo = 3.24 Å

W—W = 3.22 Å

The numerous dimeric metal carboxylates[5, 16, 18] and metal dioxides with distorted rutile structure[5, 59, 68] are also ligand-bridged systems and likewise fail to show good correlations between metal-metal distances and bond orders. Conversely, series of complexes shown by other measurements to have different bond strengths often display constant metal atom distances[143, 144]. On its own, X-ray structure analysis is not very informative here; however, its advanced application, electron-density determination[64, 145], could provide more information in the future.

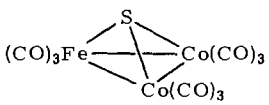
[*] Group V elements. See IUPAC Nomenclature of Inorganic Chemistry, Rule 1.21, and the Section entitled "Collective Names for Groups of Elements".

3.2. Magnetism

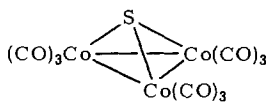
A decrease in magnetic moment from the value for isolated metal atoms in their coordination sphere is the quickest indication of a metal-metal bond. It applies almost without exception to organometallic complexes in which the metal-metal bond is nearly always associated with diamagnetism. It is only of limited validity for more "inorganic" transition metal compounds, in which diamagnetism is more often the exception then the rule and in which the reduced magnetism often comes about by superexchange *via* bridging atoms. Many metal dioxides[5, 59, 68] and carboxylates[5, 16, 18] again serve as examples for the latter effect: slight paramagnetism, temperature independent paramagnetism, antiferromagnetism, and ferromagnetism in the case of CrO_2, all occur.

Detailed papers have been published on the theory of magnetism in systems with two coupling metal atoms[26, 35, 146], on the application of the theory to complexes[23] and solids[20], or to the description of individual classes of compounds, especially copper carboxylates[18, 29]. Of great importance to the theme being discussed is the fact that there is no direct relation between magnetic coupling and the bonding interaction between two metal atoms.

NMR and ESR investigations on the nature of the metal-metal bond are sparse. The finest result was obtained in a single crystal ESR study of the paramagnetic complex *(38)* which was diluted with the isostructural diamagnetic complex *(37)*[147]. It was found that the unpaired electron of *(38)*



(37)



(38)

occupied an antibonding A_2 orbital formed from metal d-orbitals; this provides experimental proof of the metal-metal bond character of the highest occupied orbitals in such complexes.

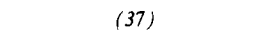
3.3. Electronic Structure

A theory of metal-metal bonding must correctly reproduce the observed structural and magnetic data. In more sophisticated form, it should also interpret the electronic spectra of polynuclear complexes or solids which have recently been studied in great detail[148, 149], and among which only the absorption for the $\sigma \rightarrow \sigma^*$ transition of single bonds[150, 151] and the $\delta \rightarrow \delta^*$ transition of quadruple bonds[152] can be assigned with comparative ease.

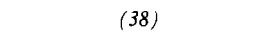
The simplest starting point is the 18-electron rule, the noble gas rule of transition metal chemistry. It governs organometallic compounds and permits ascertainment of the number of metal-metal bonds in a complex by a simple counting procedure. Systems with an odd number of electrons are rare in such cases, and only few heavy and late transition metals form 16-electron complexes.

Of similar qualitative nature and value is the skeletal electron counting method of the Wade rules[58], which was developed from the bonding theory of polyhedral boranes and links the electronic structure of organometallic clusters with their geometrical structure. In the modified form due to *Johnson*[153], the method can reproduce the shape of clusters having up to eight metal atoms[56]. An attempt at further simplification lies in the purely geometrical consideration of the space within a closely packed arrangement of ligands. Such a geometrical approach can indeed predict the shape of many clusters, independently of the bonding between the metal atoms in this space[154, 155]. The "theories" mentioned thus far do not forecast energies, but otherwise possess considerable predictive value.

Simple MO methods attempting to provide an illustrative picture of the nature of metal-metal interaction are restricted mainly to energy estimates with the aid of the symmetry properties of the metal atomic orbitals. In many cases they nevertheless afford correct correlations between the number and nature of the metal-metal bonds in complexes and clusters and the electronic configuration of the participating metal atoms. The decisive simplification consists in the complete separation of metal-ligand and metal-metal bonding. Thus, it could be shown for the structural units $Mo_3O_8^{4-}$[156], $Mo_6Cl_8^{4+}$[157], $Nb_6Cl_{12}^{2+}$ and $Ta_6Cl_{12}^{2+}$[157, 158], $Re_3X_{12}^{3-}$[157, 159], and $Re_2X_8^{2-}$[75, 160] that in each case all metal-metal bonding MOs are completely occupied by electrons. Statements about the symmetry and energy of the HOMOs in ligand-bridged dinuclear complexes were obtained analogously[161]; however, these statements did not stand up to quantitative scrutiny[162]. Finally, the predicted HOMO-LUMO nature of the metal-metal bonds of organometallic clusters could be confirmed by the ESR spectra of the complexes *(38)* and corresponding Se and Te compounds[147] and by the distinct structural differences of the Fe_4S_4 compounds *(39)*—*(41)*[163].



(39)

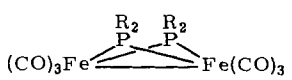


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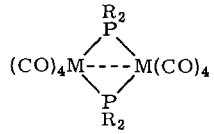


(41)

Quantitative semiempirical MO procedures, preferably the extended Hückel method (EH), are progressing towards a description of the energetics of the metal-metal bonds. This concerns the theory of magnetic interactions[146] just as much as the assignment of UV and PE spectra[164]. EH calculations have also provided a quantitative basis for the skeletal electron counting method as applied to polyhedral clusters[165] and accounted for the variation of metal-metal distance and ligand geometry in the bridged complexes *(42)*[166].



(42)



(43), M = Mn, Cr

The complicated nature of the systems preclude *ab initio* MO calculations in transition metal chemistry. Their predictive power is almost equalled, however, by two modern methods. The parameter-free approach of *Fenske* and *Hall* unequivocally demonstrated the HOMO-LUMO character and σ type of the metal-metal bonds in ligand-bridged dimers such as *(42)*[167] and *(43)*[162]. The SCF-X_α-SW procedure has also provided a very detailed description of the strong

metal-metal bonds in $Mo_2X_8^{4-}$ compounds[168,169] and the weak metal-metal bonds in the dimer $[Rh(CO)_2Cl]_2$[170] and in the tetramer *(40)*[171].

3.4. Bond Energies

Thermochemical determination of metal-metal bond energies is difficult. There are so many assumptions and simplifications to be made that the values obtained are very uncertain. Accordingly, indirect methods are still used today.

Such a method, *viz.* estimation of orbital energies, gave the highest energy value for cleavage of a chemical bond, 366 kcal/mol for the Re—Re quadruple bond of $Re_2Cl_8^{2-}$ *(9)*[75] which was subsequently reduced to 115–130 kcal/mol after a careful spectroscopic analysis[148]. Likewise indirect are determinations by way of mass spectrometric appearance potentials[172] or recombination kinetics after flash photolysis[173], which gave 25 and 36 kcal/mol for D(Mn—Mn) in $Mn_2(CO)_{10}$, as against a calorimetric value[174] of 16 kcal/mol. The values of D(Co—Co) in $Co_2(CO)_8$[174–176] also vary.

More direct information is available from equilibrium measurements in the gas phase[177] or from thermochemical measurements[174,176]; the error margin is 20—50% even in the most favorable case. The most consistent values include those recorded as activation energies of reactions proceeding *via* cleavage of the metal-metal bond[150,178]. For instance, 37 kcal/mol are required for cleavage of the Mn—Mn bond in $Mn_2(CO)_{10}$.

All determinations of metal-metal bond energies confirm the trend already discovered in the chemistry of these compounds[10,14,51] and in their mass spectra[38,179]: bonds between metals of the first transition series are extremely weak while considerable bond strengths are encountered with the heavier transition metals, and an increase in electron density at the metal atoms lowers the strength of the bond between them.

3.5. Vibrational Spectra

A convenient source of information about metal-metal bond energies should be vibrational frequencies or force constants, especially since it has been demonstrated[150,164] that these data can be correlated with the indirectly determined metal-metal bond strengths. Unfortunately, the low frequency metal-metal vibrations usually lead to very low IR intensities, and the colored substances often decompose on Raman measurements with laser light. On the other hand, the totally symmetric metal-metal stretching vibrations occasionally acquire very high intensities due to the resonance Raman effect, thus facilitating their assignment.

Metal-metal single bonds in dinuclear complexes exhibit vibrational frequencies of 150—250 cm^{-1}, corresponding to force constants of 0.5—1.5 mdyn/Å[41,53,180–182]. Frequencies and force constants show the familiar trend of increasing bond strength on going from the lighter to the heavier metals. The same applies to linear trinuclear complexes[115,183]. In these simple compounds the force constants can be calculated approximately by neglecting the ligands; this is impossible with polynuclear compounds owing to extensive coupling between metal-metal and metal-ligand vibrations[41,53].

Multiple bonds between metals appear at distinctive frequencies in the vibrational spectra. Thus a Fe—Fe double bond has a force constant of 2.7 mdyn/Å[184], and the triple and quadruple bonds in Mo and Re compounds have force constants of 3.5—4.5 mdyn/Å and vibrational frequencies of 270—400 cm^{-1}[181,185,186]. Assignment and evaluation of vibrational frequencies is more difficult in the case of clusters; however, conclusions concerning bond strengths correspond to those drawn from other measurements[41,53,181].

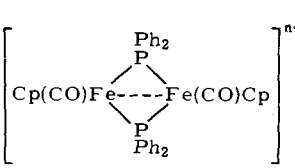
Some special applications of vibrational spectroscopy warrant mention. The most recent estimates of dissociation energies of metal-metal quadruple bonds were obtained by the Birge-Sponer approximation from overtone analysis of the corresponding Raman spectra[148]. Assignment of the $\delta \rightarrow \delta^*$ transition in the electronic spectra of complexes containing quadruple bonds was confirmed by the resonance Raman effect[187]. However, unequivocal information about bonding of the metal atoms in copper(II) acetate could not be obtained from the vibrational spectra either[181].

3.6. Variation of the Number of Electrons

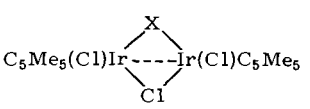
The greater the number of metal atoms linked together, the greater will be the readiness of the relevant bonds to accept unusual numbers of electrons. The excess or deficient electrons are distributed over the clusters. That this essentially amounts to variation of metal-metal interaction has been demonstrated above all for transition metal clusters containing sulfur[55]. This also provides a rational explanation for the various overall oxidation states of niobium, tantalum, molybdenum, and tungsten in octahedral M_6-halogen compounds and for the existence of paramagnetic organometallic clusters[32,56].

At the same time, polynuclear complexes become accessible to a topical method of study, *viz.* electrochemistry. Numerous electrochemical oxidations and reductions have been carried out with metal-metal linked systems in recent years[42,188]: trinuclear[189–192] and tetranuclear transition metal complexes[55,193–195] proved to be especially suitable for such studies, as did complexes with multiple bonds[196]. The effect on the metal-metal bond complied with expectation in all cases.

The resulting effects are even clearer in the few dinuclear complexes which are able to take up and release electrons reversibly[111,197,198]. This is the reason why organometallic complexes with odd numbers of electrons, such as *(19)* and *(20)*, are very rare. Experiment[188] and theory[162] concur in showing that the acquisition of two electrons means the destruction of a metal-metal bond, and *vice versa*. Accordingly, the Fe—Fe distance in complexes *(44)*[199] is 3.49 Å for $n=0$,



(44), n = 0,1,2



(45), X = H, Cl

3.12 Å for $n=1$, and 2.78 for $n=2$, and analogously in complexes *(45)*[200] 3.77 Å for X=Cl and 2.90 Å for X=H. Two electrons are removed by the oxidation process in *(44)*, and by replacement of the three-electron ligand Cl by the one-electron ligand H in *(45)*.

3.7. Cooperative Phenomena

Deep color, conductivity, and unusual magnetic properties are the physical manifestations of the transition from covalent metal-metal bonding to metallic bonding in solids (cf. Section 2.3). In this article we shall consider only the phenomena observed with infinite one-dimensional systems.

In keeping with their structure, compounds containing chains of metal atoms exhibit anisotropy in many of their physical properties. The practical potential of these compounds has prompted intensive research into such properties. Surveys have been published of optical, NMR, and ESR spectra, conductivity and superconductivity, magnetism, Mössbauer spectra, dielectric constants, and diffraction of X-rays and neutrons[21, 24, 30, 44, 54, 61]. Furthermore, the structures[24, 30, 54, 201] and theory of bonding[24, 30, 44, 61, 132, 202] of one-dimensional metals have also been studied.

Among the one-dimensional systems, significant metal-metal interactions probably occur only in the polymeric d^8 complexes. This is especially true of partially oxidized species in which all the metal atoms are equivalent, although the oxidation numbers do not have integral values. Metallic properties embracing even superconductivity are to be expected in some cases; however, distortions of the chains of metal atoms are often observed, partly in connection with the Peierls instability, which transforms the metallic conductors into semiconductors or insulators at low temperatures.

4. Chemistry of Metal-Metal Bonds

Owing to the large number of types of compounds with metal-metal bonds, it is impossible to present generally valid schemes for their synthesis or reactions. Many reactions leading to formation or breaking of metal-metal bonds are still discovered by chance. Compared with other classes of compounds, the systematic preparative chemistry of metal-metal bonds is still underdeveloped.

4.1. Synthesis

A number of conditions indicated by chemical experience have to be fulfilled for metal-metal bonds to be formed. These include relatively low oxidation states of the metals, suitable bonding partners, suitable coordination sphere, and frequently also the presence of heavy transition metals. If the metal and bonding partner are then chosen in such a way that the resulting hypothetical mononuclear species has an odd number of electrons, dimerization to form a metal-metal bond become likely. Examples of such predictable compounds are the carbonyl complexes of transition metals with an odd number of electrons[3] and the halides of the d^1 ions[19, 51].

A systematic entry to metal-metal bonds common in organometallic chemistry consists in metathetic reaction of a metal-halogen compound with an anionic metal complex. Innumerable hetero-dinuclear complexes, especially main group metal-transition metal compounds have been prepared in this way[3, 5]. The combination of two neutral complexes to form donor-acceptor metal-metal bonds also belongs to this kind of nucleophilic attack on a metal center (cf. Section 2.1.1).

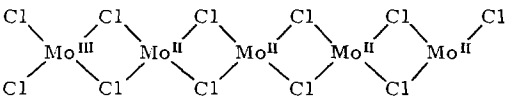
Less systematic, but no less versatile, are reactions involving elimination of bonding partners from mononuclear compounds. This method is commonly used to prepare M_2 units from carbonyl complexes or metal halides[19]. Well known examples are the formation of $Fe_2(CO)_9$ from $Fe(CO)_5$ and the formation of $[Nb_2Cl_8]_x$ from $NbCl_5$. The method of elimination must be chosen such that the desired compound does not undergo further reaction. The success rate of such reactions is enhanced if the two metal atoms are previously linked *via* a bridging ligand[203, 204]. In favorable cases, elimination can also lead to multiple bonds[33, 101, 102].

Bridging atoms can themselves induce formation of metal-metal bonds. For this to happen, bonding partners must be present or generated in the reaction system which are capable of linking together several metal atoms. In this connection, detailed studies have been performed on the PR_2 and SR groups[22], the H atom[28], and the acetylene ligand[5, 205] which stabilize many dinuclear species. Sulfur atoms have proved particularly effective in linking three metal atoms, thereby supporting cluster formation[1, 55].

The synthesis of aggregated systems is possible, in principle, by the same methods as for dinuclear units. Clusters or polymers are formed with suitable metals if a multiply unsaturated species is constructed in the presence of a substoichiometric amount of bonding partner or on simultaneous elimination of several bonding partners. In the case of halogen clusters of Nb, Ta, Mo, W, and Re this is accomplished by reduction of higher halides, which can be controlled to give the desired oxidation state or cluster form[19, 51]. The large clusters of gold[56], nickel[206], and platinum[207] are formed by reduction from simple halogen or carbonyl complexes of these metals.

Among the carbonyl complexes, elimination of CO groups is the commonest method of aggregation. It can be induced thermally, photochemically, or chemically, and the shape of the resulting cluster cannot be predicted[11, 34, 56]. Impressive examples are seen in the synthesis of osmium carbonyl clusters containing up to eight osmium atoms by pyrolysis of $Os_3(CO)_{12}$[153] and the preparation of hydride clusters by pyrolysis of carbonyl complexes in the presence of hydrogen[28, 208]. Hetero-clusters can also arise by co-aggregation of two metal carbonyl species[56].

The mode of formation of clusters cannot usually be stated; kinetic studies are available in only two cases. They suggest that transformation of $Co_2(CO)_8$ into $Co_4(CO)_{12}$ proceeds *via* elimination of CO to give $Co_2(CO)_7$ and $Co_2(CO)_6$ which then dimerizes[209]. In the reduction of molybdenum halides



(46)

to Mo_6 clusters there are indications that a Mo_5Cl_{11} chain *(46)* is initially formed which then coils up to give the

$Mo_5Cl_{13}^{2-}$ cluster which has been isolated. Addition of another Mo_1 unit then gives the final product $Mo_6Cl_{14}^{2-}$ (Fig. 2)[210a].

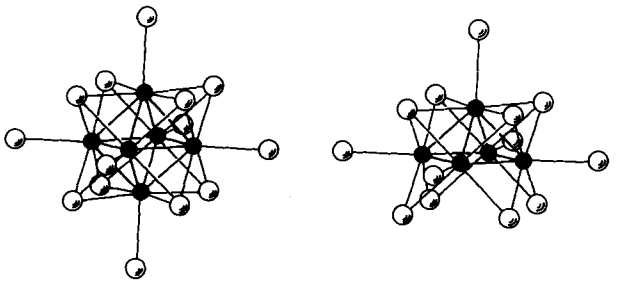


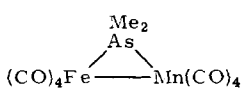
Fig. 2. Structures of the $Mo_6Cl_{14}^{2-}$ (left) and $Mo_5Cl_{13}^{2-}$ clusters (right) [210b].

As the number of known compounds with metal-metal bonds increases, so also do the number of transformations of such compounds by substitution and the number of analogous syntheses with other bonding partners. In favorable cases, the carbonyl groups of polynuclear complexes[3, 211] and clusters[56] can be replaced by two-electron donors. The same applies to the halogen ligands in octahedral halogen clusters[212] and in dinuclear complexes with quadruple bonds[16]. The synthetic methods employed, especially for "one-dimensional metals", are usually the same, *viz.* conproportionation or partial oxidation, and the physical properties are modified by systematic variation of the bonding partners[24, 30, 213, 214].

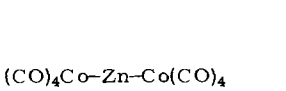
4.2. Reactions

Thorough studies of the reactions of complexes with metal-metal bonds have been limited to rearrangements and ligand substitution[3, 5, 10, 16, 32, 39, 50, 56]. Reactions directly affecting the metal-metal bond, which we shall consider in this article, have only recently attracted attention. The "softness" and variability of the metal-metal bond permits nucleophilic and electrophilic attack, homolytic and heterolytic cleavage, oxidation and reduction, the boundaries between the various reaction types often being poorly defined.

The most frequently observed reaction of the metal-metal bond is its nucleophilic degradation. This is promoted by the fact that bonding of a metal atom to a ligand nearly always liberates more energy than bonding of a metal atom to another metal atom[10, 51]. The longest known examples are seen in the disproportionation of polynuclear carbonyl complexes under the influence of hard bases[211]; however, phosphanes, acetylenes, and even CO cleave metal-metal bonds in carbonyl complexes of light transition metals[10, 32, 205, 211], the "large" clusters[11] being particularly sensitive to CO. In ligand-bridged complexes such as *(47)*, reversible cleavage by CO clearly demonstrates the weakness of the metal-metal bond[204, 215, 216]. And the tendency of complexes such as *(48)* to undergo ionic cleavage in polar solvents also correlates with the strength of their metal-metal bonds[42, 115]. The sensitivity of polynuclear complexes towards nucleophiles also raises problems in their CO substitution reactions.

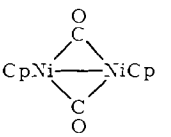


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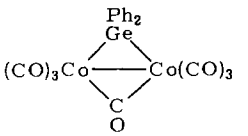


(48)

In many cases, nucleophilic attack is preceded by rupture of the metal-metal bond. This can be established by kinetic studies of the reaction course. Thus the Ni—Ni bond is broken prior to reaction of *(49)* with acetylenes[217], and the Co—Co bond prior to reaction of *(50)* with CO, phosphanes[218], or acetylenes[219]. The same applies to decomposition of $Co_4(CO)_{12}$ with acetylenes[205] and of $Ru_3(CO)_{12}$ with CO or phosphanes[220]. Even the racemization of phosphorus-bridged trinuclear complexes[221] and substitution of CO groups by phosphanes in $Mn_2(CO)_{10}$[150] proceed *via* intermediate cleavage of the metal-metal bond.



(49)



(50)

Surprisingly, even the quadruple bond of M_2X_8 compounds of molybdenum[222] and rhenium[223–225] is broken in the presence of suitable ligands. In these cases, however, the initial reaction step appears to be addition or substitution rather than cleavage of the metal-metal bond.

Further evidence for the weakness of the metal-metal bonds of the light transition metals is provided by numerous insertions of tin halides, SO_2, metals of the second subgroup, and acetylenes[42, 226, 227]. Insertion of $SnCl_2$ into *(51)* is preceded by homolysis of the Co—Co bond[228] *(vide supra)*.

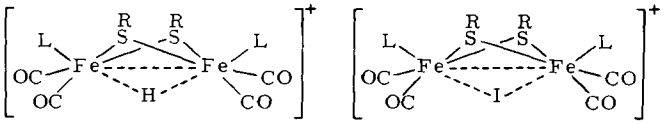
$$Bu_3P(CO)_3Co—Co(CO)_3PBu_3 \quad (51)$$

The most effective means of inducing homolysis of metal-metal bonds is photolysis. The relationship between light absorption and light-induced cleavage has been thoroughly investigated for carbonyl complexes[34, 60], and monomeric complex fragments have been identified as the photolytic primary products[173, 229]. These short-lived fragments were identified by ESR spectroscopy after trapping with nitrosodurene, *i.e.* after transformation into the stable nitroso radicals[230]. Typical chemical reactions of the fragments are abstraction of halogen atoms from chlorohydrocarbons to form organometallic halides[60, 231] or addition of potential ligands to give substituted carbonyl complexes[34, 60]. A photooxidation has been described for the complex $[CpFeCO]_4$[232].

The variations in the electron complement described in Section 3.6 also affect the metal-metal bond. The most drastic effect is cleavage of the dinuclear carbonyl complexes to form carbonylmetalate anions on chemical or electrochemical reduction[3, 188]; the slightest effect is observed on addition or removal of an electron in some clusters[17, 42, 56]. The redox chemistry of transition metal clusters has also attracted recent attention (see Section 5), not least because of its biochemical significance.

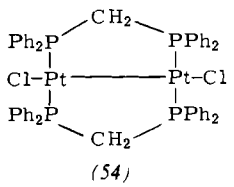
The discovery that the occupied orbitals of highest energy in the compounds under consideration are those accounting for metal-metal interactions suggests that metal-metal bonds should be nucleophilic. Accordingly, some electrophiles do indeed add to metal-metal bonds. The protonation of

clusters[10, 28] is well known; however, protonation of metal-metal bonds in dinuclear complexes is by no means rare[233–235] even though many of the known complexes with H-bridged metal-metal bonds (see Sections 2.1.2 and ref. [5]) are not formed in this way. The electrophile $HgCl_2$, which frequently forms donor-acceptor metal-metal bonds, is also capable of adding to a bond between two metal atoms[236]. Oxidative cleavage of metal-metal bonds by halogens[3, 42, 237] also seems to start with an electrophilic attack. Ionic intermediates with positively charged halogen bridges are often postulated in this connection; their resemblance to the protonated compounds is illustrated by structures *(52)*[234] and *(53)*[237].



(52) L = PR_3 *(53)*

Addition of CO to *(54)*[238] is an example of the uncommon addition of nucleophiles to metal-metal bonds without subsequent reaction. Nucleophilic cleavage *(vide supra)* is the rule: the addition of CO, phosphanes, acetylenes, allenes, and halogens to the Mo≡Mo triple bond of *(13)* is no exception[102, 239], appearing as an addition only because a Mo—Mo single bond is retained. Some of the resulting complexes are also obtained by CO substitution from $[Cp(CO)_3Mo]_2$, which itself is transformed into *(13)* on loss of CO[102].



(54)

$Cp(CO)_2Mo{\equiv}Mo(CO)_2Cp$

(13)

5. Systems Possessing Practical Potential

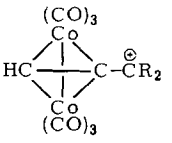
Economically the most important compound having covalent metal-metal bonds is $Co_2(CO)_8$, 25000 tons of which are employed per annum in oxo synthesis plants[240]. However, since the catalytically active species in the oxo synthesis does not contain a Co—Co bond it is outside the scope of this article. The use of other metal-metal linked compounds in engineering and the sciences is still insignificant, yet some of these hold promise of practical application in stoichiometric or catalytic organic reactions, in electronics, or in biology.

Properties of importance in this context—stabilization and activation of substrates—are also found in many metal-metal bonded complexes, and especially in clusters. Clusters show analogies with both polyfunctional mononuclear compounds and with the surfaces of metals. The following phenomena are of prime importance:

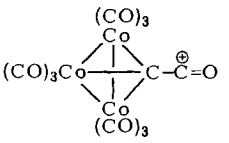
1) Polynuclear complexes can bind to unsaturated organic molecules[5, 32, 39, 46, 56]. The complexes can offer several bonding sites and form vacant coordination sites not only by substitution of ligands[39, 56], but also by cleavage of metal-metal bonds[241, 242].

2) Oxidative addition of substrates to polynuclear complexes appears to be favored by the proximity of two metal atoms. Many examples of unusual addition of H_2 and C—H bonds support this statement[28, 39, 56, 243].

3) Polynuclear complexes can act as reservoirs for excess or missing electrons[50, 56]. The two cobalt-stabilized carbocations *(55)*[244] and *(56)*[52] which can be isolated as salts are the clearest examples of this behavior.



(55)



(56)

4) Many unsaturated organic compounds bound to polynuclear compounds exhibit fluxional behavior. This leads to contacts between metal and ligand atoms which are not linked together in the rigid structure[245]. Reaction sites can be made to approach each other in this way.

5) CO groups and H atoms are also highly mobile on the surface of polynuclear complexes. They behave essentially in the same way on clusters[4, 28, 39] as on clean metal surfaces[246, 247]. In particular, $Fe_3(CO)_{12}$ fluctuates so strongly that localized bonds between iron atoms and CO groups cannot be formulated[248, 249]. In clusters containing hydrogen as ligand[28, 250] the fluctuation of the H atom is comparable with the diffusion of hydrogen through metals with regard to mechanism and activation energy.

6) The similarity between clusters and metal surfaces is substantiated by the physical finding that ligand-free clusters containing only few metal atoms have practically the same electronic work functions as the clean metals[251].

This knowledge has already been utilized in some stoichiometric and catalytic reactions. The cobalt-modification of organic compounds exemplified for *(55)* and *(56)* has led to an independent branch of chemistry dealing with acetylene-dicobalt[205] and methinyltricobalt complexes[52]; diverse organic reactions have been promoted by processes involving organometallic dinuclear complexes[252, 253]. Catalysis by clusters has been observed in isomerizations, hydrogenations, oligomerizations, and carbonylations of olefins and acetylenes; catalytically active intermediates have been isolated in several cases and it has usually been established that the clusters and not their fragments are the active species[39, 56, 205, 240, 242, 254–256]. A process for production of hydroquinone from acetylene, CO, and H_2 with $Ru_3(CO)_{12}$ as catalyst appears to have been developed to an industrial scale[240]. The renaissance of coal chemistry is also reflected in this area: it has recently been discovered that $Ru_3(CO)_{12}$ catalyzes the water gas shift reaction (a) at low temperature[257] and that $Ir_4(CO)_{12}$ is a useful catalyst for the Fischer-Tropsch synthesis (b)[258]. The cluster is not destroyed in either case.

$$CO + H_2O \rightleftarrows CO_2 + H_2 \quad (a)$$

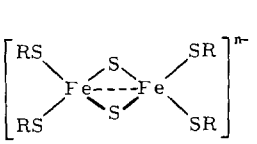
$$nCO + (2n+1)H_2 \rightarrow C_nH_{2n+2} + nH_2O \quad (b)$$

Possible uses of "one-dimensional metals", *viz.* compounds containing chains of metal atoms, lie in their postulated superconductivity and in the fact that in the ideal case they represent minute electrical conductors with their own insulation[21, 36, 44, 61]. Nevertheless, in spite of the large number

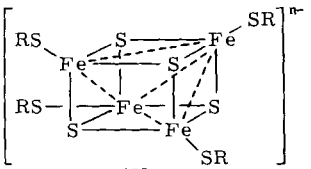
of chemical and physical studies[24, 30] the desired high-temperature superconductivity has yet to materialize, and their use as current carriers is limited by the difficulty of obtaining ideal crystals of sufficient size.

Biochemical stimuli for the study of complexes with metal-metal bonds result from the observation that biological redox systems often involve enzymes containing several metal atoms[259]. Since polynuclear complexes readily take up and release electrons (Section 3.6) it appears justifiable to assume that the active sites of the enzymes concerned are aggregates of metal atoms. Nature employes mainly iron, molybdenum, and copper for electron transfer purposes.

The best studied species are the ferredoxins and related redox enzymes. They contain the Fe_2S_2 unit *(57)* or the Fe_4S_4 unit *(58)*[260] as redox centers, these moieties having meanwhile been isolated from biological material by chemical methods[261]. *(57)* and *(58)* exist in various oxidation states, the iron atoms being equivalent in each case. Prior to and since this discovery, a large number of organometallic Fe_4S_4 and Fe_2S_2 clusters have been prepared and their redox properties investigated[42, 55]. Nevertheless, the special properties of the natural or artificial systems *(57)* and *(58)* have not yet been approximated by other systems.



(57)



(58)

The copper-containing centers in oxidases and similar enzymes are less well known[262]. The occurrence of spin-paired Cu^{II}-Cu^{II} units can be taken as proved. In enzymes and model compounds alike[263], the nature of the Cu—Cu interaction appears just as complicated as in inorganic Cu_2 complexes[18, 29].

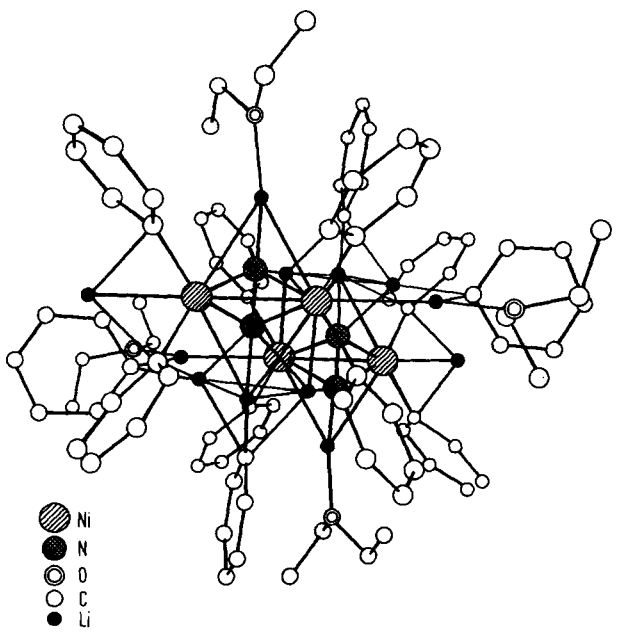


Fig. 3. Structure of the complex $[\{(PhLi)_3Ni\}_2N_2(Et_2O)_2]_2$ [267].

The greatest economic significance of metal enzyme-catalyzed reactions lies in the field of nitrogen fixation which occurs on molybdenum-containing centers[264, 265]. There has been no lack of attempts to identify the active molybdenum species or to imitate it with dinuclear complexes with and without metal-metal bonds[55, 264, 266], and yet, apart from the fact that reduction equivalents are provided by Fe_4S_4 units[261], no information has been gained about polymetallic units. However, since six reduction equivalents are required to convert the N_2 molecule into ammonia, polynuclear dinitrogen complexes are often synthesized in experiments on nitrogen reduction by metal complexes. One of the most involved results of such work, *i.e.* the compound $[\{(PhLi)_3Ni\}_2N_2(Et_2O)_2]_2$[267] (Fig. 3), closes this survey. Figure 3 once again demonstrates the validity of the introductory statement that main-group metals and subgroup metals can form metal-metal bonds among themselves and with one another.

6. Outlook

This article, which covers the literature up to the middle of 1977, is intended to throw some light on the interesting properties and the significance of the metal-metal bond. Some distinct trends should be noted: now that the existence of metal-metal bonds has been established in numerous chemical environments, preparative and structural research is concerned with larger and larger units of ever-increasing degree of aggregation. In the simple compounds, on the other hand, the ligand systems are becoming more and more diversified. Thus interest can shift from synthesis and characterization of metal-metal bonds to their reactions and effects of their ligands. Substitutions and redox reactions of polynuclear complexes and the cleavage of metal-metal bonds possess considerable synthetic potential which has hardly been utilized. Compared with bulk metals, polynuclear complexes containing metal-metal bonds are simplified models which greatly facilitate studies on the basic processes of chemisorption and substrate mobility. Compared with mononuclear complexes, on the other hand, the specific features of metal chemistry—stabilization and activation of ligands—are more pronounced. This versatility and its potential utilization justify the chemistry of the metal-metal bond.

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Tetrahedral Carbonylcobalt Clusters

By Günter Schmid[*]

Dedicated to Professor Heinrich Nöth on the occasion of his 50th birthday

A variety of general methods is available for the synthesis of tetrahedral heteronuclear cobalt clusters of type $(CO)_9Co_3E(L)_n$ (E = hetero element). The size of E has a limiting effect on the existence of such complexes. No compounds $(CO)_9Co_3E(L)_n$ have so far been prepared in which the covalent radius of E exceeds 1.30 Å. Elements such as In, Sn, Pb, Sb, or Bi do not fit into the tetrahedral Co_3E cluster unit and form open complexes $E[Co(CO)_4]_n$ ($n = 3, 4$). Structural variations among the heteronuclear clusters are encountered in the presence or absence of carbonyl bridges between the cobalt atoms: hetero atoms E bearing several ligands L favor bridging, whereas those bearing only one ligand or none at all permit terminal bonding of all the CO groups.

1. Introduction

The concept of "cluster compounds" has been variously defined since intensive research into this class of compounds began. Since the term "cluster" is also employed in astronomy, biology, solid state physics, nuclear physics, mathematics, and even in music, a precise definition of the word as used in this article is called for.

F. A. Cotton[1] defined metal clusters as species "containing a finite group of metal atoms which are held together entirely, mainly, or at least to a significant extent, by bonds directly between the metal atoms even though some non-metal atoms may be associated intimately with the cluster".

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In contrast, polynuclear complexes are compounds without metal-metal bonds. Hence $(CO)_5Mn—Mn(CO)_5$, for example, numbers among the cluster compounds, a situation which prompted *Chini* to classify such species as "open" (*e.g.* $Mn_2(CO)_{10}$) and "closed" clusters (*e.g.* $Fe_3(CO)_{12}$ or $Rh_6(CO)_{16}$)[2]. Other authors reserve the term cluster for compounds containing at least three metal atoms in direct contact or even in a cyclic array[3–5]. Subdivision into "open" and "closed" clusters has not been generally accepted. Instead, "open complexes" are usually taken to be polynuclear compounds devoid of direct interaction between the coordination centers (see Fig. 1).

In compliance with current practice and the principal points made in previous proposals, the cluster concept should be understood in the following sense: a cluster represents a group of three or more atoms, each one of which is linked to at least two of the others by chemical bonds. Hence it follows that each atom is part of at least one ring. Furthermore, this definition is not restricted to metal clusters. There are indeed many examples of cluster compounds containing not only metals but also non-metal atoms. The subconcept of a "heteronuclear cluster" is employed when the cluster unit is composed of various elements—in contrast to homonuclear clusters.

This article surveys our present knowledge of heteronuclear, tetrahedral cobalt clusters of the type $(CO)_9Co_3E(L)_n$; the heteroelement E can bear n ligands L.

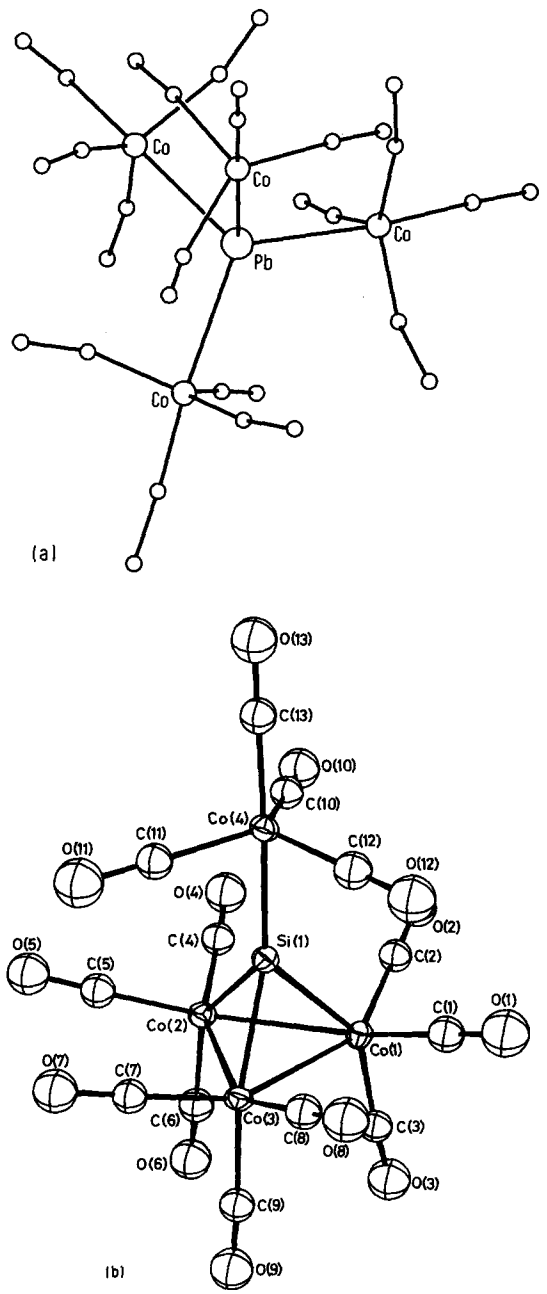


Fig. 1. Examples of (a) an open complex, $Pb[Co(CO)_4]_4$ [6], and (b) a cluster, $(CO)_9Co_3Si—Co(CO)_4$ *(10)* (see Table 2) [7].

2. Methylidyne Clusters

The oldest example of these heteronuclear carbonylcobalt clusters is methylmethylidynenonacarbonyl-*triangulo*-tricobalt which was prepared by *Cotton*[8] in 1958 and subjected to X-ray structure analysis by *Dahl* in 1967 (Fig. 2)[9]. The structure of the compound is determined by interaction of the sp^3-hybridized orbitals of the apical C atoms with suitable orbitals of the cobalt atoms. All the atoms are electronically and coordinatively saturated so that the cluster group $(CO)_9Co_3C$ always exhibits diamagnetism.

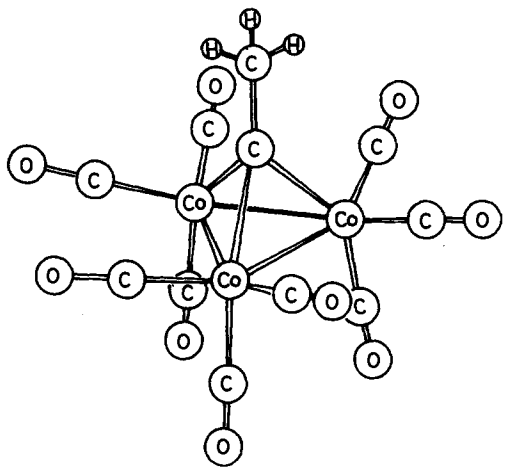


Fig. 2. Structure of $(CO)_9Co_3C—CH_3$ [type *(1)*, see Table 2] [9].

Carbon-containing clusters incorporating the μ_3-CL group are usually designated as methylidyne clusters. The ligand L can be varied almost at will; thus clusters are known with L = H, halogen, alkyl, arylalkyl, aryl, halo-alkyl or -arylalkyl, formylalkyl, and oxoalkyl[10–13] and other groups. The "organic chemistry" of the μ_3-C atom has been studied extremely thoroughly, but will not be considered in the present context.

The dark red to black methylidyne clusters are unusually stable towards air and dissolve in organic solvents. The particular stability of the Co_3C cluster unit is also manifested in the mass spectra, the Co_3C^+ fragment generally appearing at high intensity. The structure of the Co_3C tetrahedron is simple and readily understandable: the three cobalt atoms are linked by single bonds oriented at angle of 60° to each other. The $Co—C_{ap}$ distances also correspond to single bonds. The tetrahedral environment of the apical C atom is distorted because the Co—C—Co angles are *ca.* 80° on average. All the methyli-

dynenonacarbonyltricobalt clusters examined so far comply with these structural principles. A detailed account of bonding will be presented in Section 5.

3. Which Hetero-Elements Can Be Incorporated into the Co_3E Tetrahedron?

Apart from carbon, many other main group and subgroup elements might be considered as candidates for the hetero element E in the Co_3E cluster unit. One of the aims of this article is to examine which elements can be incorporated, and which cannot. The principal elements to be considered are listed in Table 1. Those elements which have already been incorporated into the cluster unit are indicated by a plus sign. A minus sign means that preparative studies gave negative results or have not yet been completed. No studies have yet been reported for the other elements.

Table 1. Compilation of the most important chemical elements that are potential hetero atom candidates E in $(CO)_9Co_3E(L)_n$. The + sign denotes: Co_3E cluster known; −: investigations negative or not yet complete; no sign: not examined.—The covalent radii [Å] [a] are given under the symbols for the elements.

							B+ 0.82	**C+** 0.77	N 0.75	O 0.73
							Al+ 1.18	**Si+** 1.11	**P+** 1.06	**S+** 1.02
Ti− 1.32	V 1.22	Cr 1.18	Mn 1.17	**Fe+** 1.17	**Co+** 1.16	**Ni+** 1.15	Ga 1.26	**Ge+** 1.22	**As+** 1.20	Se+ 1.16
Zr 1.45	Nb 1.34	**Mo+** 1.30	Tc 1.27	**Ru+** 1.25	**Rh+** 1.25	Pd 1.28	In− 1.44	Sn− 1.41	Sb− 1.40	Te− 1.36
Hf 1.44	Ta 1.34	**W+** 1.30	Re 1.28	**Os+** 1.26	Ir 1.27	Pt 1.30	Tl− 1.48	Pb− 1.47	Bi− 1.46	

[a] Partly contradictory values are given for the covalent radii of the elements in the literature. The values used here should therefore not be regarded as absolute values; instead, it is the relative size of the elements which is of interest. The relative sizes are the same in nearly all literature sources. The values of the covalent radii used in this article are taken from the "Table of Periodic Properties of the Elements", Sargent-Welch Scientific Company, Skokie, Illinois (USA).

The most important heteronuclear cobalt clusters of type $(CO)_9Co_3E(L)_n$ can be seen from Table 2.

The methylidyne clusters of type *(1)* have been synthesized in large numbers thanks to the almost unlimited variability of the ligands L. Compounds of type *(2)*—*(6)*, in which the ligand L contains an oxygen atom at the point of linkage with the methylidyne C atom, also belong to the class of methylidyne clusters ("oxomethylidyne clusters"). Only few examples of this type of compound could be listed in Table 2.

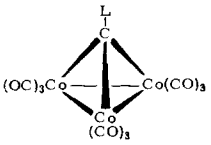
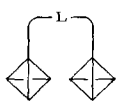
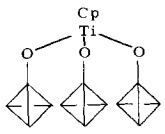
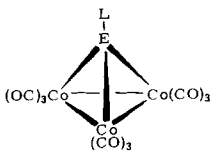
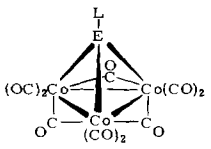
In many respects, sp^3-hybridized boron atoms resemble sp^3-hybridized carbon atoms. Thus, the existence of the boron-containing cluster $(CO)_9Co_3B—NEt_3$ *(7)* is not surprising. Attempts to synthesize the amine-free compound $(CO)_9Co_3B$ failed, apparently because the angular distortion would be too large for sp^2-hybridized boron. The reported preparation of the analogous aluminum compound $(CO)_9Co_3Al$ *(15)*[26], containing only trivalent aluminum is therefore surprising. This series of heteronuclear clusters is continued by E=S *(8)*[21,22], Se *(11)*[24], P *(9)*[23], and As *(12)*[27]. Such clusters can be expected for sulfur and selenium as well as for phosphorus and arsenic. However, the compound $(CO)_9Co_3P$ is unstable: it trimerizes with displacement of CO to give $[(CO)_8Co_3P]_3$[27]. The long-sought silicon- and germanium-containing cluster compounds *(10)*[7] and *(13)*[28] could be confirmed only very recently.

Among the transition metals, iron, ruthenium, osmium, rhodium, and nickel, as well as molybdenum and tungsten, have also been incorporated into the Co_3E tetrahedron, as has cobalt itself which forms the well-known cluster $Co_4(CO)_{12}$. Compounds $(CO)_9Co_3Co(CO)_3$ $(=Co_4(CO)_{12})$ and $(CO)_9Co_3Fe(H)(CO)_3$ *(14)*, as well as $(CO)_9Co_3Rh(CO)_3$ *(16)* and $(CO)_9Co_3Ru(H)(CO)_3$ *(17)* are isoelectronic.

Let us now consider the problem of the "non-existence" of some nonacarbonyltricobalt clusters. In spite of the incomplete experimental work, Table 1 reveals that only atoms up to a certain covalent radius are apparently capable of forming Co_3E tetrahedra. No case has yet been found in which a heteroelement with a covalent radius of more than 1.30 Å could be incorporated in the Co_3E tetrahedron. Numerous studies with, say, indium, thallium, tin, lead, antimony, bismuth, or titanium all proved unsuccessful. The futile syntheses of $(CO)_9Co_3SnL$ and $(CO)_9Co_3PbL$ clearly demonstrate that the systems avoid cluster formation, yielding instead the open complexes $Sn[Co(CO)_4]_4$ and $Pb[Co(CO)_4]_4$ (cf. Fig. 1a)[34]. Antimony and bismuth also give open complexes $(Sb[Co(CO)_4]_3$ and $Bi[Co(CO)_4]_3)$[34]. Cluster formation would involve linkage of three cobalt atoms with loss of CO. This fails to occur either on heating or on UV irradiation. Instead of the desired cluster formation, complete decomposition to CO and the metals is observed. The clusters $(CO)_9Co_3Si—Co(CO)_4$ *(10)* and $(CO)_9Co_3Ge—Co(CO)_4$ *(13)* are sublimable, being thermally stable up to 50 °C.

Tin and lead have covalent radii of 1.41 and 1.47 Å, respectively, and accordingly large Co—Sn and Co—Pb distances. Cluster formation requires the three Co atoms to approach close enough for interaction to occur. For a constant Co—Co distance this means that the Co—E—Co angle must be all the smaller the larger E becomes. Beyond a given maximum distortion, which is of course also dependent upon other increments such as the degree of hybridization, cluster formation becomes impossible, particularly since the Co_3 triangle can hardly be deformed. The Co—Co—Co angle is almost exactly 60° in all compounds. The recognizable limit of r_{cov} (E) is 1.30 Å

Table 2. The most important cobalt clusters of type $(CO)_9Co_3E(L)_n$, arranged in the order of increasing covalent radius of E. The Co_3C tetrahedra of the polynuclear complexes *(4)*—*(6)* are represented in simplified fashion. Some of the structures have been confirmed by X-ray structure analysis (see footnotes), the others being proposals.

Cpd.		E	L	Synthesis [a]	Ref.
	*(1)*		Organic group [b], H, Cl	A, C	[8–13]
	(2)		$-OBCl_2\cdot NEt_3$ [c], $-OBBr_2\cdot NEt_3$ [c, d] $-OAlCl_2\cdot NEt_3$, $-OAlBr_2\cdot NEt_3$	A, B	[14–17]
	(3)		$-OTiCl(Cp)_2$ [c, e] $-OZrCl(Cp)_2$ [c] $-OHfCl(Cp)_2$ [c]	A, B	[18,19]
	*(4)*		$-OTi(Cp)_2O-$ $-OZr(Cp)_2O-$ [c, f] $-OHf(Cp)_2O-$ [c, f]	B	[19]
	(5)		$-OTi(Cp)_2OTi(Cp)_2O-$ $-OZr(Cp)_2OZr(Cp)_2O-$ $-OHf(Cp)_2OHf(Cp)_2O-$	B	[19]
	*(6)*			B	[20]
	*(7)*	B	NEt_3	C	[16]
	(8)	S	— [c]	E	[21, 22]
	(9)	P	—	A, C	[23]
	(10)	Si	$Co(CO)_4$ [c, g]	C	[7]
	(11)	Se	— [c]	E	[24]
	(12)	As	—	A, C	[27]
	(13)	Ge	$Co(CO)_4$ [c]	C	[28]
	*(14)*	Fe	H, 3CO	E	[25]
	(15)	Al	—	C	[26]
	(16)	Rh	3CO	C	[29, 30]
	(17)	Ru	H, 3CO	A, E	[31]
	(18)	Os	H, 3CO	E	[32]
	(19)	Mo	Cp, 2CO [c, h]	D	[33]
	(20)	W	Cp, 2CO	D	[33]

[a] Syntheses A–E, see Section 4. [b] The structure of *(1)*, L = CH_3, has been confirmed by X-ray analysis (see Fig. 2). [c] Structure confirmed by X-ray analysis. [d] See Fig. 4a. [e] See Fig. 4b. [f] See Fig. 6. [g] See Fig. 1b. [h] See Fig. 7.

as already mentioned. Thus titanium (r_{cov} = 1.32 Å) already appears unsuitable for formation of the Co_3Ti cluster: all attempts at synthesis have so far failed. For example, reaction of $(\eta\text{-}C_5H_5)TiCl_3$ and $NaCo(CO)_4$ in toluene affords the open complex $(\eta\text{-}C_5H_5)Ti[OCCo_3(CO)_9]_2Co(CO)_4$ (Fig. 3). This complex contains two oxymethylidyne clusters bonded to the titanium atom which arise in hitherto unexplained manner. The third and fourth valences of titanium are occupied by a η-cyclopentadienyl and a $Co(CO)_4$ group. This shows that Ti—Co bonds are indeed stable.

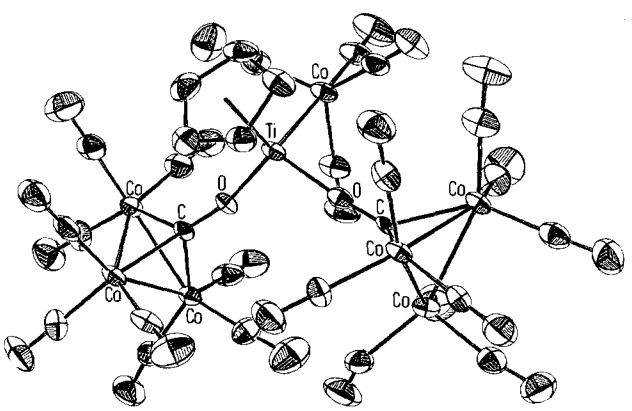


Fig. 3. Structure of $(\eta\text{-}C_5H_5)Ti[OCCo_3(CO)_9]_2Co(CO)_4$ [35].

4. Syntheses

Several pathways are available for the synthesis of tetrahedral heteronuclear cobalt clusters. The synthetic procedures A—E (cf. Table 2) will now be considered (X = Halogen, H).

A $\quad Co_2(CO)_8 + X_mEL_n$

B $\quad \begin{cases} [(CO)_9Co_3CO]^- + X_mER_n, \\ \text{replacement of R in } (CO)_9Co_3COER_n \end{cases}$

C $\quad [(CO)_4Co]^- + X_mEL_n$

D $\quad$ Thermolysis/photolysis of $(CO)_4Co—EL_n$

E $\quad$ Others

4.1. Method A

Method A is the method of choice for synthesis of methylidyne clusters of type *(1)*:

$$4X_3CL + 9Co_2(CO)_8 \rightarrow \underset{(1)}{4(CO)_9Co_3CL} + 6CoX_2 + 36CO \qquad (a)$$

X = Halogen

The first methylidyne cluster (L = CH_3) was prepared in this way (Fig. 2). The whole spectrum of methylidyne clusters becomes accessible by variation of L. Surprisingly, methylidyne clusters are also formed on reaction with element halides

X_mER_n with E = B, Al, Si, or Ti, which display Lewis acid character. Examples are found for compounds of type *(2)* and *(3)* in Table 2. They are all oxymethylidyne clusters, *i.e.* species containing μ_3-CO moieties. Figures 4a and 4b show the structure of a compound of type *(2)* and one of type *(3)*.

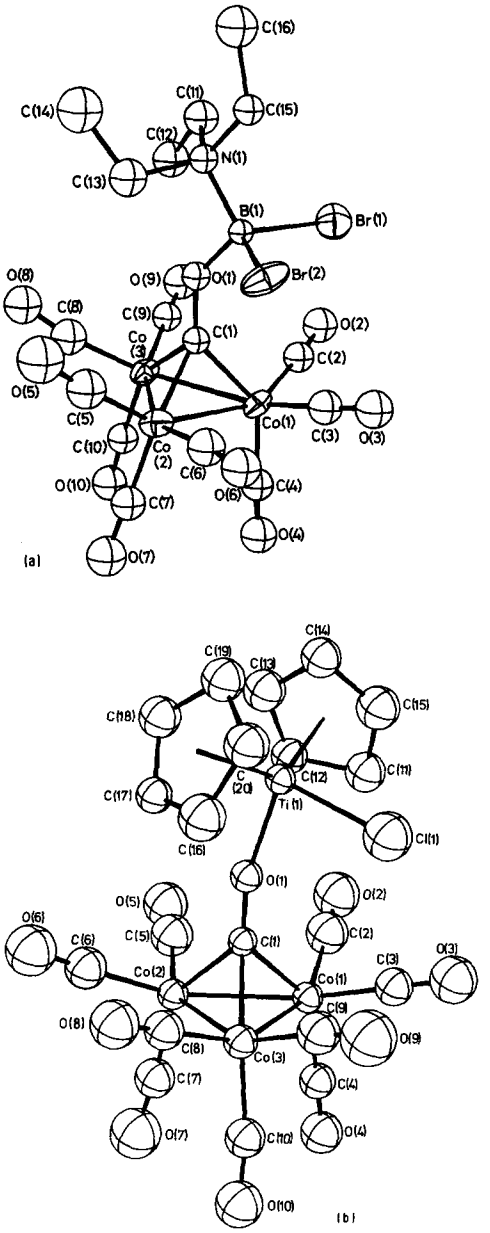


Fig. 4. Structures of the oxymethylidyne clusters (a) $(CO)_9Co_3COBBr_2 \cdot NEt_3$ [type *(2)*] [17] and (b) $(CO)_9Co_3COTi(Cl)(\eta\text{-}C_5H_5)_2$ [type *(3)*] [18].

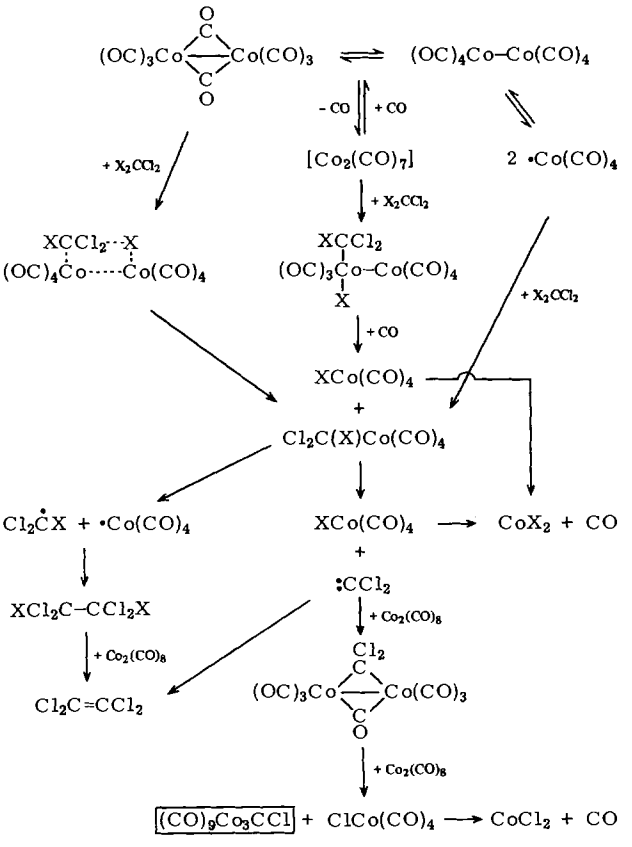
Equations (b) and (c) show the idealized reaction courses:

$$4Et_3N \cdot BBr_3 + 7Co_2(CO)_8 \rightarrow 4(CO)_9Co_3COBBr_2 \cdot NEt_3 + 2CoBr_2 + 16CO \quad (b)$$

$$4(\eta\text{-}C_5H_5)_2TiCl_2 + 7Co_2(CO)_8 \rightarrow 4(CO)_9Co_3COTi(Cl)(\eta\text{-}C_5H_5)_2 + 2CoCl_2 + 16CO \quad (c)$$

Reactions (b) and (c) follow a completely different course from (a). While the C atom of X_3CL is incorporated into the tetrahedral cluster according to reaction (a), E is transferred from X_mER_n into a component of the ligand L in $(CO)_9Co_3CL$ ($L = OB(halogen)_2 \cdot NEt_3$, $OAl(halogen)_2 \cdot NEt_3$, $OSiR_3$, $OTi(Cl)Cp_2$, *etc.*). The μ_3-CO group therefore comes from the octacarbonyldicobalt.

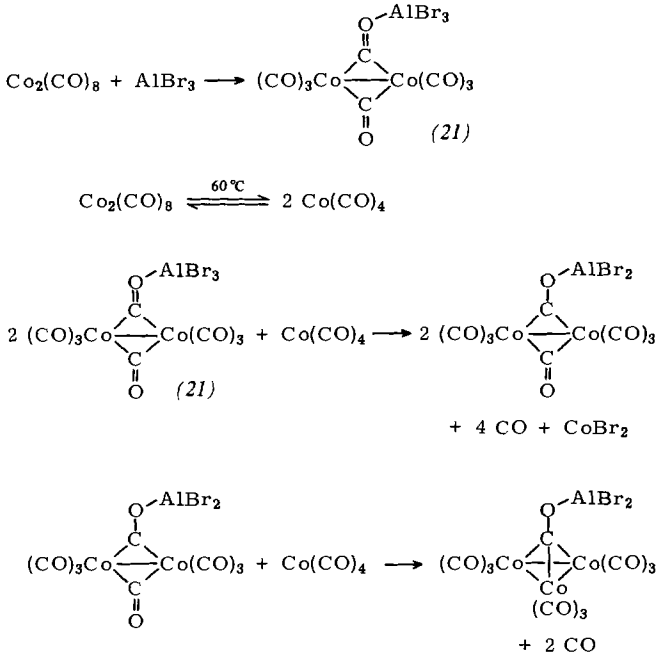
For reactions between $Co_2(CO)_8$ and chlorinated hydrocarbons in nonpolar solvents, *Haszeldine et al.*[36] proposed a mechanism involving carbenes as reactive intermediates: Both the reaction of $Co_2(CO)_8$ with CCl_4 and the reaction with $CBrCl_3$ or CBr_2Cl_2 afford not only the methylidyne cluster $(CO)_9Co_3CCl$ but also tetrachloroethylene. If the reaction is carried out with CCl_4 in the presence of excess cyclohexene, the yield of $(CO)_9Co_3CCl$ falls from 41 to 29%. In addition 7,7-dichloronorcarane can also be detected. Similar findings have been reported for the reactions of $Co_2(CO)_8$ with $CBrCl_3$ or CBr_2Cl_2 in the presence of cyclohexene. The basic reaction steps on formation of $(CO)_9Co_3CCl$ from $Co_2(CO)_8$ and X_2CCl_2 are shown in Scheme 1.



Scheme 1.

Starting from the known equilibrium between bridged and unbridged $Co_2(CO)_8$ the dichloromethane derivative X_2CCl_2 can attack in three possible ways: 1) X_2CCl_2 is added oxidatively to $(CO)_4Co—Co(CO)_4$ *via* a four-center mechanism; 2) X_2CCl_2 likewise undergoes oxidative addition but only to one Co atom; 3) oxidative addition only takes place after homolysis of $Co_2(CO)_8$ to $Co(CO)_4$ radicals. The $XCo(CO)_4$ formed in each case is known to be unstable, decomposing to CoX_2 and CO. The crucial step is formation of dichlorocarbene from $Cl_2C(X)Co(CO)_4$. Some of the carbene dimerizes to tetrachloroethylene, and some inserts between the two Co atoms of $Co_2(CO)_8$. Formation of the Co—C bonds is then followed by renewed reaction with $Co_2(CO)_8$ to give $(CO)_9Co_3CCl$ as final product.

In contrast, completely different reactions must take place on formation of oxymethylidyne clusters. Of decisive importance for the overall reaction course in the present case of reaction with X_2CCl_2 and of X_mER_n with $Co_2(CO)_8$ are the initial interactions. While oxidative addition of carbon to cobalt occurs in the former case, the compounds X_mER_n (E = B, Al, Si, Ti) act as Lewis acids in the second case, interacting with the oxygen atom of a bridging carbonyl group. Isolation or spectroscopic detection of primary products such as $(CO)_8Co_2 \cdot AlBr_3$ *(21)*[14] demonstrates that the initial reaction steps are due to Lewis acid-base interactions. Similar interactions can also be assumed to occur in other Lewis acid element halides such as $XSiR_3$ or $(\eta\text{-}C_5H_5)_2TiCl_2$. Scheme 2 shows a possible mechanism for the reaction of $AlBr_3$ with $Co_2(CO)_8$ which has not been proved in every detail but should be broadly valid and also apply to other Lewis acids.



Scheme 2.

Although the amine adducts $X_3B \cdot NEt_3$ and $X_3Al \cdot NEt_3$, which no longer exhibit Lewis acid properties, are used for the synthesis of $(CO)_9Co_3COEX_2 \cdot NEt_3$ (E = B, Al) [type *(2)*], the adducts undergo partial dissociation at 60 °C (*i.e.* at the reaction temperature) into NEt_3 and EX_3. Homolysis of $Co_2(CO)_8$ into $Co(CO)_4$ radicals is also feasible under the reaction conditions.

4.2. Method B

The synthesis of some oxymethylidyne clusters is also possible by method B, which starts from an existing $(CO)_9Co_3CO$ skeleton. The boron and silicon compounds $(CO)_9Co_3COBH_2 \cdot NEt_3$[37] and $(CO)_9Co_3COSiR_3$[37] (R = CH_3, Ph) were obtained for the first time by this method *via* the alkali metal compounds $[(CO)_9Co_3CO]M$. The synthesis of the first ester containing the cluster group $(CO)_9Co_3C$ (Fig. 5) was accomplished by reaction of $[(CO)_9Co_3CO]Li$ with acetyl bromide[38]:

$$[(CO)_9Co_3CO]Li + BrCOCH_3 \rightarrow (CO)_9Co_3CO{-}COCH_3 + LiBr \quad (d)$$

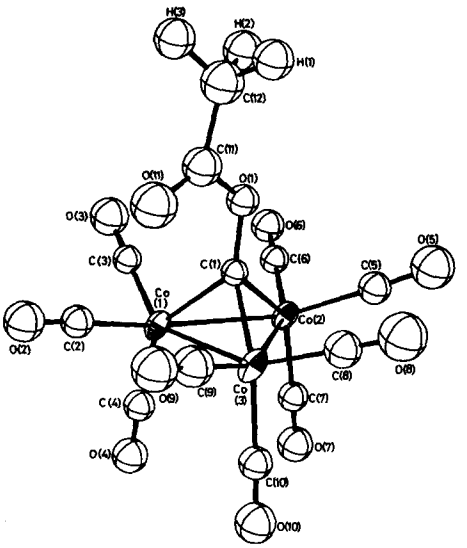


Fig. 5. Structure of $(CO)_9Co_3CO{-}COCH_3$ [38].

Method B also permits the synthesis of a variety of transition metal derivatives of types *(3)*, *(4)* (cf. Fig. 6), *(5)*, and *(6)*.

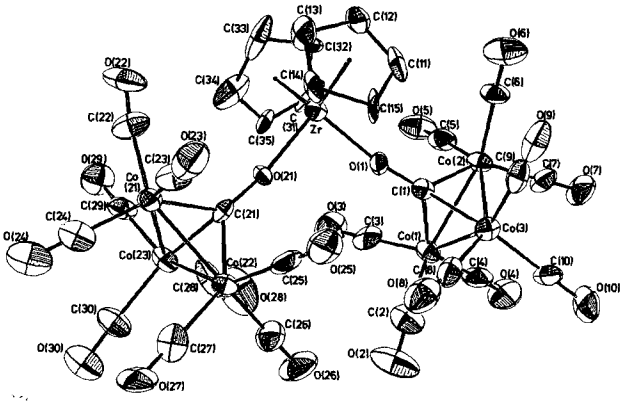


Fig. 6. Structure of $[(CO)_9Co_3CO]_2Zr(\eta\text{-}C_5H_5)_2$ and the analogous hafnium compound [type *(4)*] [19].

In some cases replacement of groups R in $(CO)_9Co_3COER_n$ compounds gave compounds accessible with difficulty, if at all, by other methods: *e.g.*, $(CO)_9Co_3COBr_2 \cdot NEt_3$ by fluorination of the analogous bromine compound with $AgBF_4$[7] and compounds *(5)* by hydrolysis of compounds *(3)*[19]:

$$2(CO)_9Co_3COE(Cl)Cp_2 + 2\,NaOH \rightarrow \underset{(3)}{} \underset{(5)}{[(CO)_9Co_3COECp_2]_2O} + 2\,NaCl + H_2O \quad (e)$$

(5)

E = Ti, Zr, Hf

4.3. Method C

Reaction between the carbonylcobaltate ions $[(CO)_4Co]^-$ and element halides is of broad scope (method C). It generally leads to formation of cobalt-element bonds, a prerequisite for the formation of heteronuclear cluster compounds $(CO)_9Co_3E(L)_n$. Numerous methylidyne clusters of type *(1)* which are also accessible by method A can be prepared by

method C. In recent years, particular attention has been focused on syntheses of heteronuclear clusters with elements E other than carbon. Thus, once the first methylidyne clusters had been synthesized, the search began immediately for homologous silanetriyl clusters $(CO)_9Co_3SiL$; and syntheses of compounds containing boron, aluminum, germanium, phosphorus, and arsenic appeared as the obvious next step. As discussed in Section 4.1, halogen compounds of boron and aluminum, and also silicon react with $Co_2(CO)_8$ to give oxymethylidyne clusters. If interactions between Lewis acids and the O atom of a bridging carbonyl group are prevented by use of $[Co(CO)_4]^-$ then the desired complexes can indeed be obtained by method C. Formation of clusters is presumably preceded by generation of open complexes:

$$SiI_4 + 4[Co(CO)_4]^- \rightarrow Si[Co(CO)_4]_4 + 4I^- \quad (f)$$

$$Si[Co(CO)_4]_4 \rightarrow (CO)_9Co_3Si{-}Co(CO)_4 + 3CO \quad (g)$$

(10)

The possible intermediacy of $(CO)_9Co_3Si{-}I$ receives some support from mass spectrometric studies; this would mean that the cluster is formed from the open complex $[(CO)_4Co]_3$-SiI. Corresponding proposals are also possible for the synthesis of compounds of boron *(7)*, aluminum *(15)*, germanium *(13)*, phosphorus *(9)*, and arsenic *(12)*, particularly since the open complexes of the homologs indium, $In[Co(CO)_4]_3$, tin and lead, $M[Co(CO)_4]_4$[6], and antimony and bismuth, $M[Co(CO)_4]_3$[34] are isolable. It is nevertheless surprising that $Co_2(CO)_8$ can also react with PX_3 and AsX_3[27]. These halides do not react to give methylidyne clusters but form P- or As-containing clusters. Apparently the Lewis acidity of these halides towards the bridging carbonyl oxygens in $Co_2(CO)_8$ is not large enough, so that P—O and As—O interaction fails to occur. This is impressively demonstrated by experiments in which the reactions of $[(CO)_9Co_3CO]Li$ with halophosphanes were studied. Surprisingly, eq. (i) applies instead of eq. (h)[39]:

$$[(CO)_9Co_3CO]Li + ClPPh_2 \not\rightarrow (CO)_9Co_3COPPh_2 + LiCl \quad (h)$$

$$[Co(CO)_4]^-Li^+ + ClPPh_2 \rightarrow Ph_2PCo(CO)_4 + LiCl \quad (i)$$

The origin of $[Co(CO)_4]^-$ in ethereal solutions of $[(CO)_9Co_3$-$CO]Li$[40] is still unclear; however, equilibration appears a possibility especially since evidence has been obtained in favor of a species $Co_2(CO)_6$ in solution[41]:

$$[(CO)_9Co_3CO]^- \overset{Solv.}{\rightleftharpoons} [Co(CO)_4]^- + Co_2(CO)_6(Solv.)_n \quad (j)$$

Solv. = solvent

On the other hand, it cannot be ruled out that $Li[Co(CO)_4]$ is already formed on production of $[(CO)_9Co_3CO]Li$. Whatever the reason may be, the finding that $ClPPh_2$ selects the second component from a solution containing $[(CO)_9Co_3$-$CO]Li$ and $Li[Co(CO)_4]$ shows that phosphorus avoids bonding to the oxygen, preferring interaction with cobalt instead. The same most likely applies to arsenic.

4.4. Method D

Formation of compounds *(19)* (Fig. 7) and *(20)* has been well studied[33]:

$$(CO)_3CpECl + [Co(CO)_4]^- \rightarrow (CO)_3CpE{-}Co(CO)_4 + Cl^- \quad (k)$$

$$3(CO)_3CpE{-}Co(CO)_4 \rightarrow (CO)_9Co_3E(CO)_2Cp + 4CO + [(CO)_3Cp{=}E]_2 \quad (l)$$

(19), (20)

E = Mo, W

Although the actual cluster formation in method D proceeds as shown in eq. (l), the decisive step is formation of the Co—E bond according eq. (k). The "open" intermediates postulated for boron, aluminum, silicon, or phosphorus can be isolated here. This substantiates the proposed reaction course of cluster formation according to method C.

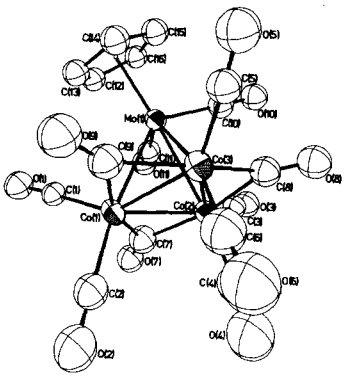


Fig. 7. Structure of $(CO)_9Co_3Mo(CO)_2(\eta\text{-}C_5H_5)$ *(19)* [33].

4.5. Other Methods

The syntheses of some cluster compounds with transition elements and with sulfur and selenium as hetero atoms do not fit into the series of methods mentioned.

These methods are designated as "E" in Table 2. $(CO)_9Co_3S$ *(8)* can be prepared just as well from $Co_2(CO)_8$ and sulfur in hydrocarbons as from $Co_2(CO)_8$ and CoS or H_2S. Relatively high yields are even obtained with thiophenol and $Co_2(CO)_8$. The homologous selenium compound *(11)* is formed from H_2Se and $Co_2(CO)_8$ in hexane at 150 °C and 100 atm[10].

Some cluster compounds of type $(CO)_9Co_3E(H)(CO)_3$ [*(14)*, E = Fe; *(17)*, E = Ru; *(18)*, E = Os] are formed in a highly complicated way. Thus $Fe(CO)_5$ and $Co_2(CO)_8$ in acetone react to give $[Co(CH_3COCH_3)_3][FeCo_3(CO)_{12}]_2$, which affords the iron compound *(14)* with conc. HCl or H_2SO_4[25]. It is isoelectronic with the known compound $Co_4(CO)_{12}$. The ruthenium compound *(17)* is formed analogously or from $Co_2(CO)_8$ and $[Ru(CO)_3Cl_2]_2$[31], while the osmium compound *(18)* is obtained from Na_3OsCl_6, CO, and $Co_2(CO)_8$[32].

5. Chemical Bond and Structure

Many attempts have been made to describe the chemical bond in metal clusters. *Dahl et al.* have developed a highly detailed concept of the bonding in heteronuclear clusters of the type $(CO)_9Co_3E$ on the basis of LCAO-MO models[24], which will now be briefly considered. Assuming the Co_3E tetrahedron to have ideal C_{3v} symmetry, the metal orbitals

available for metal-metal bonding can be constructed as shown in Figure 8. For this purpose each Co atom is placed at the origin of a system of Cartesian coordinates. The positive z-axes are directed towards the centroid of the triangle, the y-axes are perpendicular to the angular surface, and the x-axes are situated in the Co_3 surface.

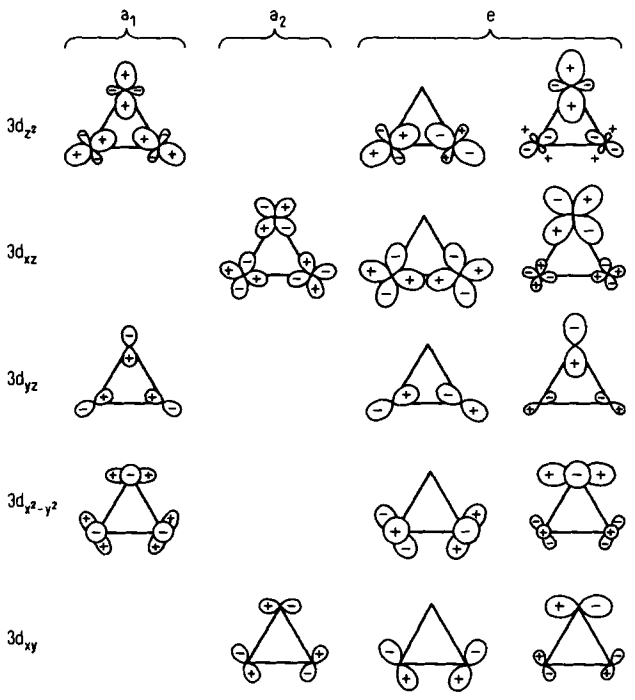


Fig. 8. Overlapping of 3d orbitals of three Co atoms in the Co_3 triangle.

This model reproduces the bonding in a greatly simplified, but qualitatively correct manner. Combinations of the three 4s- and nine 4p-orbitals possess the correct symmetry for formation of σ bonds, both to the CO groups and to the hetero atom E. Ignorance of the extent of mixing precludes our stating the energetic sequence of the Co_3 orbitals.

Table 2 shows that there are two types of compounds $(CO)_9Co_3E(L)_n$, which differ in the arrangement of the CO groups. Carbonyl bridges occur if the hetero element is a transition metal. (The structure of the Co_3Mo cluster *(19)* is confirmed—see Fig. 7—the correctness of the structural proposals *(14)*, *(16)*—*(18)*, and *(20)* is assumed; *(15)* *(vide infra)* is a special case.)

The problem of the formation of carbonyl bridges in carbonylmetal compounds is still unsolved. To this day, there is no firm experimental evidence for one or the other concept.

It is readily appreciated that the reason for the occurrence of carbonyl bridges in the $Co_3E(L)_n$ system must be sought in the nature of E or the EL_n group because the remainder of the tetrahedron, the Co_3 plane, is not subject to change. In the compounds $(CO)_9Co_3E(L)_n$ without carbonyl bridges, *e.g. (7)*—*(13)*, the three terminal CO groups of each cobalt atom can adopt an almost ideal mutual arrangement, thus minimizing repulsion (Fig. 9a). However, if the hetero atom itself bears three CO groups, as is the case in the complexes with E = Fe, Co, Rh, Ru, and Os, then perturbing interactions will occur between these three CO groups and a total of six upward-directed CO groups of the three cobalt atoms ($3 \times C^1$, $3 \times C^2$). As a result, C^2 is folded down into the Co_3 plane. In the direction of E, C^1 can adopt an orientation between two of the three terminal CO groups of E (Fig. 9b). In this way the two CO groups of all four metal atoms of the cluster adopt an overall distorted icosahedral arrangement.

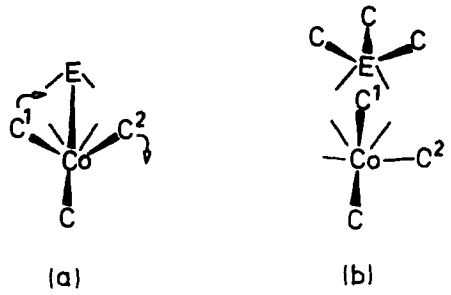


Fig. 9. Representation of the geometrical situation in (a) unbridged and (b) bridged complexes $(CO)_9Co_3E(L)_n$.

This idea does not explain why complexes such as $Ir_4(CO)_{12}$ do not contain bridging carbonyl groups. In this case, however, the size of the metal atoms probably also plays a role, the increasing metal-metal bond lengths on going from metals of the 1st to those of the 2nd and 3rd transition metal periods gradually prevents formation of CO bridges. This is especially apparent on comparison of homologous compounds such as $Fe_3(CO)_{12}$ with $Ru_3(CO)_{12}$ and $Os_3(CO)_{12}$ as well as $Co_4(CO)_{12}$ with $Ir_4(CO)_{12}$: bridged structures exist for iron and cobalt and non-bridged structures for the larger elements Ru, Os, and Ir.

Purely steric effects thus appear to be responsible for the formation of CO bridges. Electronic effects are not expected to play any predominant effect, although a slight gain in energy will be associated with CO bridge formation: A *pentahapto* bonded C_5H_5 ring will still cause an inversion process in the sense of Figures 9a and 9b, as seen for the example of $(\eta\text{-}C_5H_5)NiCo_3(CO)_9$[42]. On the other hand, ligands attached to the carbon, boron, silicon, or germanium do not hinder the terminal arrangement of the CO groups. The compound $(CO)_9Co_3Al$ *(15)* is an exception, for which a structure with CO bridges has been proposed[26]. This proposal should be re-examined.

6. Summary and Outlook

The present article was intended to summarize the present state of knowledge in the field of tetrahedral heteronuclear cobalt clusters of the type $(CO)_9Co_3E(L)_n$. Owing to their simple and readily comprehensive structures, the compounds are very suitable for systematic investigations. Failure to synthesize Co_3E with a series of certain main group and subgroup elements was attributed to geometrical factors. Thus the covalent radius of E has a crucial effect on the existence of the cluster. Further studies should enable us to test this hypothesis.

Another important finding resulting from the systematic study of these complexes concerns the presence or absence of carbonyl bridges in the Co_3 plane. The reasons are probably to be sought in the steric requirements of $E(L)_n$. This could be of general validity for carbonylmetal compounds. The complexes $(CO)_9Co_3E(L)_n$ possess, as the first carbonylmetal compounds, a directing group $E(L)_n$ which can promote or suppress

bridge formation. This assumption also requires substantiation by further preparative and structural studies.

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The Distribution of Charge in Complex Compounds

By Joseph Chatt and G. Jeffery Leigh[*]

The charges on metal atoms and ligands in complex compounds of transition metals may be calculated theoretically or measured empirically, but there is no reliable method of doing either. This review is concerned mainly with two experimental methods, dipole moment measurement and X-ray photoelectron spectroscopy, applied to tertiary phosphane and such complexes of the heavier transition metals. It is concluded that the charge is rarely greater than $\pm 0.3e$ and that some so-called neutral or positive ligands, *e.g.* N_2 or NO^+, may carry more negative charge in a complex than formally anionic ligands such as H^-. Small ligands of high formal charge, *e.g.* O^{2-}, NR^{2-}, and N^{3-}, appear to carry no more negative charge than Cl^-, but monoanionic ligands vary greatly in their capacity to contribute to the dipole moments. The ligands NO, CO, PF_3, CH_3^-, and H^- are all nearly neutral to slightly negative, whereas pyridines, tertiary phosphanes, *etc.* are the most strongly positively charged.

1. Introduction

We have been interested for some time in the way in which charge is partitioned between the various partners (metal and ligands) in a metal complex. There is no direct way of measuring the absolute charge on an atom in a compound, but there are a variety of ways in which information bearing on it can be arrived at by calculation or empirically; also there is a large amount of chemical experience which is summed up by rules of thumb, such as the Pauling Electroneutrality Principle which suggests that the charge on an atom in a complex will generally lie between +1 and −1, whatever the formal charges.

It is, of course, possible to calculate charges at atomic centers if the appropriate wave functions (or molecular orbital coefficients) are known. Thus charge distributions can be calculated from any measurable property that can be related to wave functions or molecular orbital coefficients. In practice,

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the correlation with wave functions is not easy, and calculations of charge distributions are not often related to empirical measurements. Further, calculations involving transition metal complexes are often suspect. One is thus left with empirical methods for more accessible and reliable determination of charge distribution.

The experimental techniques which give information about charge distribution can be conveniently considered under a variety of headings. There are those which look directly at atomic nuclei, nuclear quadrupole resonance (NQR) and the Mössbauer effect. In NQR the quadrupole coupling constants may be related to the occupancy of p- or d-orbitals, and this, in turn, is affected by the ionic/covalent character of the various bonds. NQR evidence supports the idea of electron transfer by π-bonding to d-orbitals in complexes of early transition elements. The Mössbauer isomer shifts are also related to charge density at the nucleus, and depend upon metal oxidation state, coordination number, and spin state. However, the precise interpretation in terms of charge distribution is very difficult. The Mössbauer quadrupole splitting is also difficult to interpret in these terms.

A second set of empirical techniques investigates the electronic energy levels. Included in this heading are UV and X-ray photoelectron spectroscopy, X-ray spectroscopy, and electronic spectroscopy in various forms. Of these spectroscopic methods we shall discuss only X-ray photoelectron spectroscopy in any detail. The information concerning charge distribution contained in data obtained using any of these spectroscopic techniques is often not easily accessible.

Finally, we have techniques which measure electron distribution throughout a whole molecule. Foremost is X-ray structure analysis, which is, however, generally of too low a resolution to enable us to look at minor variations in valence-electron distribution. Magnetic resonance techniques are also amenable but the data are again often not easily analyzed. Nevertheless, ESR spectroscopy provided early evidence of electron transfer from the p-orbitals of chloride ligands into the d-orbitals of the later transition metals in high oxidation states as in $[IrCl_6]^{2-}$. Magnetic neutron diffraction promises to be of great value in determining the distribution of unpaired electrons, but is unlikely to be of general availability. There is, however, a further, much older technique which has been comparatively ignored in recent years. The dipole moment of a molecule is a gross measure of its electrical asymmetry. Whereas the dipole moment of a complex compound has often been taken as a criterion of its stereochemistry, the significance of the moment as a measure of charge distribution has been much less frequently considered. The purpose of this review is to discuss the extent to which a relatively new technique (XPS) and a relatively old technique (dipole moment measurements) can give information regarding the charge distribution in complex compounds.

2. Measurement of Dipole Moments

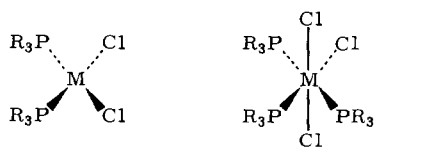
The dipole moment of a complex can be considered as the vector sum of components operating along the axes of the complex. The values for single axial moments (group moments) can be elucidated by suitable choice of complex, and Table 1 gives a list of calculated P—M—Cl group moments based on a simple vectorial analysis[1,2]. There is a slight dependence on whether the phosphanes are aromatic or aliphatic, but nevertheless the narrow range of group moments, 6.8 ± 0.9 D, implies that the charges on P and Cl are approximately constant. The significance of this constancy will be discussed below. However, there is a problem in converting these group moments to individual charges as reflected by a point-charge model. This is that individual bond moments cannot be easily determined. Even where the dimensions of the molecule are known, there is of course still no guarantee that a point charge model is an accurate representation, but it is difficult to use a more complete model and we shall therefore use the simpler one.

Table 1. Dipole moments and P—M—Cl group moments [D] for various complexes.

Complex	Observed dipole moment	Ref.	P—M—Cl group moment
cis-$[PtCl_2(PEt_3)_2]$	10.7	[41]	7.6
mer-$[RuCl_3(PEt_2Ph)_3]$	6.9	[42]	6.9
mer-$[RhCl_3(PEt_2Ph)_3]$	7.3	[43]	7.3
mer-$[RhCl_3(PEt_3)_3]$	7.0	[43]	7.0
mer-$[ReCl_3(PEt_2Ph)_3]$	6.3	[28b]	6.3
mer-$[IrCl_3(PEt_3)_3]$	6.9	[44]	6.9
cis-$[RuCl_2(Et_2PCH_2CH_2PEt_2)_2]$	9.8	[45]	7.0
cis-$[RuCl_2(Ph_2PCH_2CH_2PPh_2)_2]$	9.5	[45]	6.8
cis-$[OsCl_2(Et_2PCH_2CH_2PEt_2)_2]$	9.3	[45]	6.6
cis-$[OsCl_2(Ph_2PCH_2CH_2PPh_2)_2]$	8.3	[45]	5.9

Chatt et al. analyzed the dipole moments of a large series of compounds on the basis that a metal-halogen bond moment is 2—3 D. Even though the grounds for selecting this value were shown to be wrong[1], the general self-consistency of the analyses leaves no doubt that, to a first approximation, this magnitude of the moment is correct and can be applied to a wide range of complexes. It is not clear, however, what it means in terms of charge distribution.

Dipole moments can, however, be further analyzed. Let us assume that a pair of ligands such as a tertiary phosphane and a chloride in a *trans*-arrangement carry a charge x and y, respectively. It is not, in fact, as we shall show below, justified to assume that the charges are constant, but it does seem to be the case for complexes of the Third Transition Series. Thus in *cis*-$[PtCl_2(PEt_3)_2]$, the charge on the platinum will be $-2(x+y)$. Now consider *mer*-$[MCl_3(PR_3)_3]$. In this case the charge on the metal should be $-3(x+y)$. However, the observed moment of the complex is still equal to the group moment P—M—Cl because of the symmetry.



cis-$[MCl_2(PR_3)_2]$ *mer*-$[MCl_3(PR_3)_3]$

This group moment can only be equal to that inferred from a square planar complex if $2(x+y)=3(x+y)$, *i.e.* if $x+y=0$. Since the group moments are indeed consistent it follows that in the chloro-tertiary phosphane complexes, where there are equal numbers of PR_3 and chloride ligands, the

charges on the phosphane and on the chloride are equal and opposite. Considering the appropriate bond lengths leads to charges of +0.3 e and −0.3 e on phosphorus and halide, respectively[1].

Having thus established some magnitudes, it is possible to extend the charge assessment as follows. In Table 2 are presented some Cl—M—CO group moments. Where the Cl—M—CO group moments can be inferred directly from the molecular moment due to the axial symmetry, then it is found consistently that Cl—M—CO has a value of 2—3 D. This implies that CO is a weak donor, considerably less so than a tertiary phosphane, and it may even be withdrawing charge, as it is believed to do in $[Ni(CO)_4]$. Other data in Table 2 suggest that CO and NO carry about the same charge and that the H ligand in hydrido-complexes is slightly positive. Thus, it has been suggested that the halide ion in a *trans* position to a hydride, as in *trans*-$[PtClH(PEt_3)_2]$, has become more negative or ionic, a manifestation of the *trans* effect of the hydride[3].

By this kind of analysis, it has been possible to infer something about charge separation and charge location in highly dipolar compounds[2].

To obtain good dipole moment data it is necessary to have non-labile, non-ionic, complexes without a center of symmetry and soluble in an inorganic solvent, preferably a non-polar one such as benzene. This has tended to focus attention on the tertiary phosphane and such complexes of the heavier transition metals, particularly of Group VIII. Within this limitation, the dependence of dipole moments on the formal charges and types of ligands, and the gross inferences from them concerning charge distribution have been evaluated and summarized[2], and will be listed here.

2.1. Dependence of Dipole Moment on the Metal

The group moment P—M—Cl is generally 6—7 D. The aliphatic phosphanes tend to produce apparently slightly higher group moments than the more electronegative aromatic phosphanes. The exact metal involved is not of any significance.

2.2. Dependence on So-called Electrically Neutral Ligands

"Good" electron donors, *e.g.* tertiary phosphanes, arsanes, stibanes, pyridines and amines, *etc.*, give analogous complexes of almost equal moments. "Poor" donors, *e.g.* good back-bonding ligands such as CO and PF_3, give complexes analogous to those of the good donors but with moderate moments. Thus *cis*-$[PtCl_2(PEt_3)_2]$ has a moment of 10.7 D, but *cis*-$[PtCl_2(CO)_2]$ has a moment of 4.65 D, close to the value expected from the Pt—Cl contributions alone. Generally such ligands as CO, PF_3, N_2, and even the so-called NO^+, appear to be negative, neutral or only slightly positive in their complex compounds. It follows that whereas the metal atom in *cis*-$[PtCl_2(PEt_3)_2]$ is about neutral, in a complex such as *cis*-$[PtCl_2(CO)_2]$ it should be considerably more positive. Also quite high charge separation is found in complex compounds containing only "neutral" ligands, *e.g.* $[Ni(CO)_2\{o\text{-}C_6H_4(PEt_2)_2\}]$ has a moment of 5.4 D.

2.3. Dependence on Anionic Ligands

Axially symmetrical complexes of type *trans*-$[PtXY(PEt_3)_2]$ where X and Y are different monovalent, anionic ligands can have considerable dipole moments, *e.g.* when X = H and Y = NCS the moment is 7.4 D, *i.e.* higher than the R_3P—Pt—Cl group moments. The negative contribution to the moments increases in the order H < Me < Ph < Cl < Br < I < NO_3 < NCS. If the Pt—H bond is arbitrarily given a contribution of zero to the moment the others contribute Me, 0.8; Ph, 1.6; Cl, 4.2; Br, 4.5; I, 4.9; NO_3, 6.8; NCS, 7.3 D. Even allowing for disparity in the sizes of the anions they obviously carry very different negative charges. Note that the contributions of the Cl, Br, and I ligands to the M—X bond moments are the reverse of those expected on

Table 2. Dipole moments and group moments [D] involving Cl, CO, NO, and H ligands in various complexes.

Complex	Observed dipole moment	Ref.	Group moment		Relation of dipole and group moments
trans-$[RhCl(CO)(PEt_2Ph)_2]$	2.4	[46]	Cl—M—CO	2.4	Equivalent
trans-$[IrCl(CO)(PEt_2Ph)_2]$	2.1	[47]	Cl—M—CO	2.1	Equivalent
trans-$[IrCl(CO)(PPh_3)_2]$	2.1	[47]	Cl—M—CO	2.1	Equivalent
trans-$[ReCl(CO)(PMe_2Ph)_4]$	2.0	[48]	Cl—M—CO	2.0	Equivalent
mer-trans-$[RhCl_3(CO)(PEt_2Ph)_2]$	3.6	[46]	Cl—M—CO	3.6	Equivalent
mer-trans-$[IrCl_3(CO)(PEt_3)_2]$	2.8	[47]	Cl—M—CO	2.8	Equivalent
mer-cis-$[RuCl_2(CO)(PEt_2Ph)_3]$	7.5	[42]	Cl—M—CO	4.7	Inferred
cis-cis-trans-$[OsCl_2(CO)_2(PEt_2Ph)_2]$	4.3	[49]	Cl—M—CO	3.0	Inferred
fac-cis-$[IrCl_3(CO)(Pn\text{-}Bu_3)_2]$	12.4	[47]	Cl—M—CO	8.1	Inferred
cis-$[PtCl_2(CO)(Pn\text{-}Pr_3)]$	10.2	[50]	Cl—M—CO	6.6	Inferred
cis-$[PtCl_2(CO)(PEt_3)]$	10.0	[50]	Cl—M—CO	6.5	Inferred
cis-$[PtCl_2(CO)_2]$	4.7	[51]	Cl—M—CO	3.4	Inferred
trans-$[PtClH(PEt_3)_2]$	4.2	[52]	Cl—M—H	4.2	Equivalent
trans-$[PtClH(PPh_3)_2]$	4.4	[52]	Cl—M—H	4.4	Equivalent
trans-$[RuClH(Me_2PCH_2CH_2PMe_2)_2]$	4.8	[53]	Cl—M—H	4.8	Equivalent
trans-$[OsClH(Me_2PCH_2CH_2PMe_2)_2]$	5.1	[53]	Cl—M—H	5.1	Equivalent
trans-$[FeClH(Et_2PCH_2CH_2PEt_2)_2]$	4.3	[54]	Cl—M—H	4.3	Equivalent
mer-cis-$[IrCl_3(CO)(PEt_3)_2]$	9.5	[47]	P—M—CO	6.8	Inferred
$[W(CO)_5(PH_3)]$	1.1	[55]	P—M—CO	4.1	Equivalent
$[Cr(CO)_5(PPh_3)]$	5.5	[56]	P—M—CO	5.5	Equivalent
$[Fe(CO)_4(PPh_3)]$	5.1	[57]	P—M—CO	5.1	Equivalent
mer-trans-$[RuCl_3(NO)(PEt_3)_2]$	2.8	[58]	Cl—M—NO	2.8	Equivalent
mer-cis-$[ReCl_2(NO)(PEt_2Ph)_3]$	6.3	[59]	Cl—M—NO	0	Inferred

the basis of relative electronegativities; they may possibly be rationalized as the effect of roughly constant absolute charges and increasing atomic radii.

2.4. Dependence on the Formal Anionic Charge

It might be expected that if a chloride ligand were replaced by formally more negatively charged ligands, such as oxide, nitride, or an organo-imide (RN^{2-}), a greater M—X bond moment would result. In fact, such complexes as *trans*-$[ReCl_3X(PR_3)_2]$ (X = Cl or O) have almost identical dipole moments. Such comparisons indicate that the Cl^-, the O^{2-}, and N^{3-} ligands make about the same contribution to the dipole moment. To obtain stable oxo-, imido-, and nitrido-complexes it is necessary to have central atoms such as rhenium in high oxidation states; then covalency is so strong that the bonds to the polyvalent anions are essentially triple in character and no more dipolar than the M—Cl bond.

In summary, dipole moments indicate that good electron donors such as amine and tertiary phosphanes in heavy transition metal complexes of type $[MCl_nL_n]$ carry considerable positive charge (≈ 0.3 e), the chloride ligands about equal negative charge, and the metal zero charge. Poor donors, *e.g.* good back-bonders such as CO, are about neutral overall under similar circumstances. This requires the metal to carry positive charge balancing that on the chlorine atoms. The contribution of monovalent anionic ligands to total charge separation in a complex varies considerably and will be a function of the size as well as the absolute charge on the ligand atom. The formal charge on the anionic ligand appears to be of no consequence so far as the dipolar quality of the M—X bond is concerned; Cl^-, O^{2-}, and N^{3-} as ligands make about equal contributions to the M—X bond moments.

3. X-Ray Photoelectron Spectroscopy

Because dipole moments measure overall separation of charge, inferences concerning absolute charges on atoms or groups can only be approximate and general. However, some of the inferences are confirmed by XPS data as detailed below.

From the beginning of XPS studies attempts have been made to relate measured binding energies to atomic charges[4]. This has never been entirely satisfactory, as evidenced by the calculations of charge which are still appearing[5]. It is evident that for the highest precision XPS measurements should be made in the gas phase, and for some complex compounds this is now possible. For example, it has been shown that the carbon atoms in volatile metallocenes have binding energies in the range 289.82, $[Co(C_5H_5)_2]$ to 290.17 eV, $[Mn(C_5H_5)_2]$, and the corresponding charges have been estimated as -0.3 e and $+0.1$ e per carbon atom[6]. The uncertainties in the binding energy measurements are estimated to be ± 0.05 eV, whereas measurements made on solids, which include the majority of complex compounds, normally have an experimental uncertainty of at least ± 0.3 eV.

The measured binding energy of an electron in a solid compound is the sum of contributions from several sources. To a first approximation we can divide these into effects due to atoms, ions, or molecules other than those due to the particular atom under study, and effects due to the atom being ionized. The former group of effects are generally classified as the Madelung contribution. The latter is a function of atomic charge, oxidation state, *etc.* The most superficial analyses of changes in binding energy generally ignore the Madelung contribution, and attempt to correlate binding energy directly with charge. This appears to be justified for the purpose of comparing binding energies of the same atoms in series of complexes of analogous types, as indicated by the consistency of the inferences which can be made from the observations.

3.1. Tertiary Phosphanes as Ligands

Tertiary phosphanes are normally believed to be π-bonding ligands—that is, they place charge onto a metal as a consequence of the partial transfer of the lone-pair electrons, and they receive charge back from metal d- or dp-hybrid orbitals into the empty 3d-orbitals of the phosphorus. In such circumstances, the total charge on the phosphorus will be the sum of these two opposing effects. One of the first endeavors of researchers using XPS has been to discover how P(2p) binding energies depend upon coordination. In fact, the results are not clear cut, and the P(2p) binding energy for PPh_3 is itself not precisely defined. The $P(2p_{3/2})$ binding energies for PPh_3, Ph_3PO, $[NiCl_2(PPh_3)_2]$, $[PdCl_2(PPh_3)_2]$ and $[CdCl_2(PPh_3)_2]$ have been reported[7] to be 131.9 ± 0.4, 132.9 ± 0.1, 131.6 ± 0.3, 131.7 ± 0.1, and 131.6 ± 0.2 eV, respectively (internal C(1s) as standard, 285.0 eV). These values seem to indicate that there is not much difference in charge between free and complexed triphenylphosphane. Independently, the $P(2p_{3/2})$ binding energies for $[MnCl(CO)_4(PPh_3)]$ and $[RhCl(CO)(PPh_3)_2]$ have been determined to be 131.2 and 131.6 eV, respectively (internal C(1s) apparently standard at 285 eV)[8]. The value for free triphenylphosphane was found to be 130.6 eV in this study. The reason for the discrepancy between the two results is not clear, but this kind of occurrence is common in XPS comparisons. Nevertheless, triphenylphosphane appears to carry the same charge as the free phosphane in all these complexes, and this is considerably less positive than in Ph_3PO; it is not clear whether phosphorus in the complexes is neutral or positive.

In an extension of this work, the complexes $[PdX_2(PPh_3)_2]$ (X = Br, Cl, I, or CN) have been studied. The $P(2p_{3/2})$ values are 131.8 ± 0.1, 131.8 ± 0.2, 131.6 ± 0.2 and 131.9 ± 0.2 eV, respectively (C(1s) graphite internal as reference)[9]. This constancy of energy is explained by a balancing of σ and π effects, which are in fact different for each X. Also the Pd(3d) energies do not vary significantly, which indicates a remarkable balancing of charges. This is consistent with the dipole moment measurements.

A considerable range of Pt complexes has also been investigated. These include a series of related triphenylphosphane complexes containing Pt^0 and Pt^{II} of general formula $[Pt(PPh_3)_2L]$, (L = $(PPh_3)_2$, PPh_3, Ph_2C_2, CO_3, O_2, CO, $C_2(CN)_4$ or Cl_2)[10]. The $P(2p_{3/2})$ binding energies were found to be essentially constant (*ca.* 131.6 ± 0.2 eV) despite the changes in Pt oxidation state and the wide variations of ligand type L. The Pt(4f) binding energies varied considerably over a range of about 2 eV. It was assumed, perhaps unwisely, that the metal atom in $[Pt(PPh_3)_2(PPh_3)_2]$ carries zero charge.

This is difficult to prove. Nevertheless, it does seem that any change in charge resulting from changes in L and in metal oxidation state is restricted to Pt and L. The phosphorus apparently achieves the same condition regardless of coordination circumstances when bound to Pd or Pt.

As a consequence of these considerations, it has been considered that PPh_3 places no charge on a metal to which it coordinates, as in, *e.g.*, $[MoCl_2(NO)_2(PPh_3)_2]$[11]. Since it is, however, a neutral molecule, and a bond is formed between PPh_3 and a metal, neutrality must imply equal and opposite σ- and π-effects. It now seems probable, in accord with the inference from dipole moments, that there is actually an overall *positive* charge on the phosphorus and that it is constant in these complexes[12]. The figure of 131.9 eV quoted above for free PPh_3 may be too high owing to oxidation of the measured sample[13]. The general indication is that, with the heavier transition elements, phosphorus in phosphane ligands *seems* to reach the same condition regardless of where it is coordinated. We shall return to this later.

An attempt has been made to settle the question of charge by use of infrared as well as XPS spectroscopy[12]. It was found for a series of benzene derivatives C_6H_5X that the intensity of ν(CH) is linearly related to C(1s) electron binding energies. The intensity of ν(CH) has been shown elsewhere to parallel the electron density on the aromatic ring. Implicit in this study, however, is a rejection of the idea normally axiomatic for crude XPS that internal C(1s) is immutable at 285.0 eV. In this case it was necessary to use a further external standard (Pt). The authors conclude that C(1s) in PPh_3 is 284.9 eV (cf. C(1s) in C_6H_6 is 284.5 eV and in $[PtCl_2(PPh_3)_2]$ is 285.3 eV). This is taken to indicate a small but real net flow of negative charge from PPh_3 to Pt. Further, it would seem that the overall charge donated from the aromatic rings on a single PPh_3 is 0.14 electrons. What the phosphorus itself donates is not clear. However, two points are apparent: (a) that C(1s) is not constant, but because the shifts are within the normal limits of experimental error, C(1s) = 285.0 eV is not a bad approximation, and (b) that even where P($2p_{3/2}$) does not change upon coordination (*e.g.*, PPh_3, 131.3 ± 0.3 eV, $[Hg(PPh_3)_2I_2]$, 131.3 ± 0.3 eV)[13] it does not *necessarily* mean that there is no overall phosphane-to-metal charge transfer. In fact, we are inclined to believe that there is. The P($2p_{3/2}$) binding energy, particularly when referenced against internal C(1s), takes no account of electron donation from the organic substituents which may change C(1s) and leave P($2p_{3/2}$) unaffected. Further, if we suppose that C(1s) does increase, indicating charge donation, by, for the sake of argument, 1 eV, then P($2p_{3/2}$) referenced to it could also increase by 1 eV but appear unchanged. The apparent constancy of the P($2p_{3/2}$) binding energies may indicate a constant C(1s)—P($2p_{3/2}$) separation within experimental error, rather than a constant charge on the phosphorus and may be consistent with the donation of negative charge from phosphorus.

There has been no wide-ranging study of the effect of changing "organic" substituents on the donor power of phosphorus, but for the heavier transition elements at least there is no sign of any systematic change: PEt_3 and PMe_2Ph seem substantially the same. Thus, for $[MCl_4(PEt_3)_2]$ (M = W, Re, Os, Ir, or Pt) and $[MCl_4(PMe_2Ph)_2]$ the P($2p_{3/2}$) binding energies fall within the ranges 131.5 ± 0.3 eV and 131.9 ± 0.2 eV (internal C(1s) standard). Considering the errors, these are identical[14]. Further, for a range of complexes $[ReCl_x(N_2)_y(PMe_2Ph)_{6-x-y}]$ ($x = y = 1$; $x = 2$, 3 or 4, and $y = 0$) P($2p_{3/2}$) is within the range 131.7 ± 0.4 eV. Evidently, nothing conclusive can be gleaned from these figures, although dipole moments show consistently that aromatic phosphanes give slightly less dipolar complexes than the aliphatic.

In a range of twenty four molybdenum complexes, generally of molybdenum(0) but with various phosphanes, P($2p_{3/2}$) was found to vary between extreme limits of 129.1 and 131.3 eV (external standard, Au)[15]. If the two extremes are excluded, the range is only 129.5 to 130.6 eV. At least one interpretation of these numbers is that generally the phosphorus reaches the same electronic condition in its complexes regardless of where it coordinates. This may be less true when phosphanes are coordinated to nickel. In that case P($2p_{3/2}$) apparently depends both upon the substituents on P and upon the metal oxidation state (*e.g.* $[Ni\{PPh(OEt)_2\}_4]$, 131.2; $[Ni\{PPh(OEt)_2\}_2(CN)_2]$, 132.3; $[Ni\{P(OMe)_3\}_4]$, 132.2; $[Ni(PPh_3)_3]$, 131.3 eV: all ± 0.3 eV, internal C(1s) = 285.0 eV)[16, 17]. Once errors are included the variations are less impressive than at first sight, and there are always reservations concerning photo-damage, particularly with First Transition Series elements. If there is a real difference between the phosphanes in nickel complexes on the one hand and in molybdenum and the heaviest metal complexes on the other, it could be explained on the basis that nickel is by far the least polarizable and it cannot so easily satisfy the charge requirements of its ligands.

3.2. Chlorine as a Ligand

The XPS method would seem to be ideal for distinguishing between the various types of chlorine (bridging, terminal, axial, equatorial, *etc.*) which can be found in metal complexes. Whether the technique can reliably do so is actually not clear. In octahedral complexes, no easy distinction can be made between facial and meridional chlorines[14]. It would seem unequivocal that the charge on a "free" chloride ion, as in a KCl lattice, should be greater than in a complex, as in $K_2[PtCl_4]$[18]. It was reported very early that the Cl($2p_{3/2}$) binding energies were 201.2 and 200.7 eV, respectively. This difference is hardly significant[19]. A study of bridging and terminal chlorines in platinum complexes led to the conclusion that the binding energy for $Cl_{bridging}$ is lower than for $Cl_{terminal}$ (*e.g.*, *trans*-$[Pt_2Cl_4(PnPr_3)_2]$, $Cl_b = 197.0$, $Cl_t = 198.2$ eV)[20]. This is not what one might expect intuitively, since a bridging chlorine, with two donor bonds, should be more positive than a terminal one. In $[Mo_2Cl_{10}]$, however, apparently the converse is true[19]. In clusters and systems containing metal-metal bonds $Cl_b > Cl_t$, but the differences are often close to the significant limits[21]. In fact all three situations $Cl_b \approx Cl_t$, $Cl_b < Cl_t$, and $Cl_b > Cl_t$ occur and the significance of these observations is doubtful.

None of these results gives a direct idea as to how much charge a chlorine atom in a complex might take up. However, an indirect approach is possible. There is a linear relationship between metal binding energy and formal oxidation state for complexes $[MCl_x(PMe_2Ph)_y]$ ($x = 2$, 3 or 4; $x + y = 6$)[1, 21]. This kind of relationship is intuitively attractive. To a first

approximation, the slope of these lines for M = W, Re, Os, and Ir appears to be 1.4 eV/unit oxidation state. Rough calculation suggests that the change of charge on the metal upon oxidation by one unit of oxidation state is nearer 0.1 electrons than 1.0 electrons[23]. In this context, "oxidation" means the exchange of a tertiary phosphane for a chlorine atom; the net effect of this is to change the binding energy by 1.4 eV.

It is possible to apportion this binding energy change to the effects of individual ligands. Thus comparison of the five-coordinate species $[ReCl_2N(PEtPh_2)_2]$ and $[ReCl_2(NO)(PMePh_2)_2]$ with the six-coordinates species $[ReCl_2N(PMe_2Ph)_3]$ and $[ReCl_2(NO)(PMe_2Ph)_3]$ respectively shows that the addition of a phosphane ligand is tantamount to the reduction of the metal by three quarters to one unit of oxidation state[1]. The addition of a chlorine atom apparently raises the metal binding energy by less than 0.5 eV. Experimental errors in binding energy measurements are such that this does not necessarily conflict with the equal and opposite charges on phosphorus and chlorine implied by the dipole moment measurements. Appropriate comparisons of the above sort allow the following inferences to be made[1, 22]. Ligating nitrogen oxide (even "NO^+", carbon monoxide, and dinitrogen are electron withdrawing in the order $NO > CO \approx N_2$. Nitrido-ligands carry less real charge than NO. Chlorine atoms are apparently roughly neutral to slightly electron withdrawing, but chloride ions are definitely electron donating. Hydrido ligands carry very little negative charge, and the metal atoms in polyhydrido complexes of very high formal oxidation state carry charges considerably less than the oxidation states might suggest[23]. Thus, the Os^{IV} in $[OsH_4(PMe_2Ph)_4]$ $[Os(4f_{7/2}) = 50.5\,eV]$ is about as positive as Os^{II} in $[OsCl_2(PMe_2Ph)_4]$ $[Os(4f_{7/2}) = 50.7\,eV]$. Pure metals often have binding energies which are consistent with complexes in oxidation states as high as +II. This may be a result of the enormous differences in structure (and hence Madelung term) between a metal and its complexes[23].

3.3. Charges on Metals in Complexes

Attempts have been made to correlate metal binding energies directly with charge on the metal. The charge is usually calculated by approximate methods, such as CNDO, Hückel, and Pauling methods. There is no independent verification of these charges, which appear to be roughly linearly related to binding energies. Thus, in a series of chromium complexes the charge was calculated (extended Hückel) to vary from zero (Cr metal) through *ca.* 1.5 ($[Cr(CO)_6]$) to *ca.* 2.5 ($[CrO_4]^{2-}$)[24]. For molybdenum, calculations indicate that it varies (Pauling) from zero (Mo metal and $MoSe_2$) through *ca.* 1 ($MoCl_5$) to 1.6 (MoO_3)[24]. For nickel, the calculated charges (Pauling) vary from zero (Ni metal) through *ca.* 0.5 ($NiCl_2$) to 1.3 (NiF_2)[16]. The linearity of the binding energy/charge relationships is comforting. The absolute values of the calculated charges are probably not very significant.

Sherwood[25] has attempted to calculate binding energies in chromium compounds on the basis of the various methods of estimating charge. He concludes that Cr in $[Cr(CO)_6]$ probably has a gross positive charge (*ca.* 1.9), carbon is just negative and oxygen considerably negative, consistent with calculations for other carbonyls (*e.g.*, $[Ni(CO)_4]$[26]). Apparently CNDO charges give calculated binding energies in better agreement with experiment than the Pauling methods[25]. The CNDO charges are presumably therefore better approximations to the truth.

The calculated charges show rough parallels with metal oxidation state. In certain very restricted circumstances (*e.g.*, where the changes from one compound to another in a series involves the exchange of the same neutral ligand with the same anion) the parallel may be close. In general, it is dangerous to assume any relationship between metal charge and metal oxidation state. Thus, Cl and O atoms apparently have the same overall electron withdrawing effect on molybdenum[27]. Consequently the metal binding energies in complexes $[MoCl_2O_2L_2]$, $[MoCl_3OL_2]$, and $[MoCl_4L_2]$ (L = neutral ligand) are about equal, despite the fact that the molybdenum oxidation states are VI, V, and IV. This accords with the evidence from the dipole moments of rhenium complexes[28] which is also supported by XPS measurements[29].

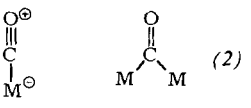
3.4. Carbon Monoxide as a Ligand

3.4.1. Terminal Carbon Monoxide

The charge on CO in metal carbonyls has long been a favorite topic of organometallic chemists. An early XPS study on $[Cr(CO)_6]$, $[Fe(CO)_5]$, and $[Ni(CO)_4]$ suggested an overall electron transfer from metal to ligand[30]. (In contrast, the cyclopentadienyl rings in ferrocene were reckoned to be slightly positive[26].) The bulk of the negative charge transferred to the CO was assumed to reside on the carbon, but this conclusion rests heavily upon the reference used for C(1s). Another XPS study on these carbonyls (and $[W(CO)_6]$) came to a similar conclusion[31], and this is now supported by calculation[26]. Thus, in $[Ni(CO)_4]$ as compared with CO, the charge on C decreases from +0.371 e to +0.234 e, and that on O increases from −0.371 e to −0.350 e. The total charge on nickel was calculated to be +0.466 e. In $[Cr(CO)_6]$ the charges on chromium, carbon, and oxygen were calculated as +0.703 e, +0.233 e, and −0.349 e, respectively. Our XPS studies also show that CO is an overall electron acceptor[1].

3.4.2. Bridging Carbon Monoxide

Carbon monoxide can bind to metals in at least three ways, the most usual being *via* the carbon atom. Much more rarely it can bind *via* oxygen, but frequently it can bind (*via* carbon) between metals (bridging) as well as terminally. It was deduced from the spectra of gaseous $[Mn(COMe)(CO)_5]$ and $[Co_4(CO)_{12}]$ that the binding energies O(1s) in bridging carbonyls are lower than in terminal ones[32]. This accords with the authors' simple valence bond representations of the



(1) *(2)*

two bonding types [see *(1)* and *(2)*], but in view of the above discussion it is difficult to accept that oxygen in a terminal carbonyl is really positive.

3.5. Nitrogen Oxide as a Ligand

Nitrogen-containing compounds have been studied intensively by XPS since the technique was first introduced. Correlations of charge with N(1s) binding energies have been attempted (see, for example, reference [33]). The charge calculated depends very much upon the method of calculation. Thus extended Hückel charges on nitrogen range from +2.6 ($NaNO_3$) to −1.7 (KSCN). The corresponding CNDO charge for $NaNO_3$ is +0.4[31]. These are not, however, the only attempts to calculate binding energies (see, for example, reference[34]). Nevertheless, it has remained tempting to use XPS to investigate the binding of NO to metals, particularly in an attempt to distinguish straight and bent forms (so-called "NO^+" and "NO^-").

It is not surprising that NO in negative ions generally carries a negative charge as in the series $[M(CN)_5(NO)]^{n-}$ (M = Mn, Cr, M, or V) although in $[Fe(CN)_5(NO)]^{2-}$ it appears to be positive[35]. The substitution method[1] seems to show that NO, even in neutral complexes, is electron withdrawing, and more strongly so than CO. A study of an extended series of metal nitrosyls suggested that bent nitrosyls (NO^-) have relatively low N(1s) binding energies whereas straight nitrosyls (NO^+) can have higher or lower N(1s) depending upon the extent of π bonding[36]. A study involving $[MoCl_2(NO)_2(PPh_3)_2]$ was taken to show that the two NO groups together remove about 0.14 electrons from the molybdenum[11]. The quantitative interpretation may be wrong, but the qualitative conclusion is probably correct. Finally a study of iridium complexes led to the startling conclusion that "NO^+" in $[IrH(NO)(PPh_3)_3]^+$ carries more negative charge than "NO^-" in $[IrCl(CO)(NO)(PPh_3)_2]^+$[37]. There is no doubt that both ν(NO) and N(1s) are unreliable for distinguishing the two kinds of NO coordination, but they can be distinguished[38] using a method which is equally applicable to sulfoxide complexes[39]. The *difference* between N(1s) and O(1s) is 132±1 eV for straight nitrosyl ligands and 128±2 eV for bent ones. Although NO^- may carry greater positive charge than NO^+, the difference in binding energies appears characteristic of the structural type.

4. Conclusions

Both dipole moment measurements and XPS provide data concerning charge distribution in complex molecules. Where they can be easily interpreted, the data are in general agreement and sufficient data are now available to allow an appreciation of gross charge distribution. Surprising factors are that both the so-called neutral and anionic ligands vary considerably in their abilities to acquire positive or negative charges respectively. This is so marked that there is a complete gradation from the strong capacity of such ligands as the tertiary phosphanes and pyridines to carry positive charge through intermediate ligands (CH_3^-, CO, H^-, N_2, NO^+, and PF_3) around zero charge, to those with a strong capacity to carry negative charge, such as halide, O^{2-}, N^{3-}, and $RCOO^-$. This appears to accord with general chemical experience. It explains such observations as that $[PtMe_2(PEt_3)_2]$ oxidatively adds methyl iodide whereas $[PtI_2(PEt_3)_2]$ does not[40], because the platinum atom in the former is more negatively charged than in the latter where the negative charge has been passed on to the iodine ligands. For the same reason, polyhydride tertiary phosphane complexes behave much more like metal(0) complexes than do the corresponding chlorides. The actual charges carried by the metal and ligand atoms in complex compounds are considerably closer to zero than are implied by their formal oxidation states; it appears that they are rarely, if ever, outside the range ±0.5 e and more often around ±0.3 e for complexes between good electron donors and acceptors[*].

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[*] At the XVIII. I.C.C.C. (1977), *F. Gallais* described work from his laboratory concerning Main Group element complexes of the type A·B (A = electron donor molecule such as Me_3As, OEt_2, *etc.*, B = electron acceptor such as $AlCl_3$, $GaCl_3$, *etc.*). The study of ^{1}H-NMR and NQR shifts suggest that the charge transfer in such complexes is also often of the order 0.3 e.

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Hemoglobin—An Inspiration for Research In Coordination Chemistry

By Johann Walter Buchler[*]

Dedicated to Professor Heinrich Nöth on the occasion of his 50th birthday

Hemoglobin transports oxygen in the blood and is responsible for its red color. Being one of the most closely studied proteins, it is entitled an "honorary enzyme". This admirable natural substance invites chemists to copy it, imitate it, and vary or modify it. The first means a total synthesis of the original molecule, but such reproduction does not increase our knowledge of its function. In the case of imitation, the biochemical effect of the "original" (*i.e.* hemoglobin) is achieved in full or in part with simpler molecules of similar structure, *i.e.* with models. Research is here directed at the function of hemoglobin. In the case of variation or modification the original molecule is changed to various extents, which reveals the factors underlying its action. In all three cases—reproduction, imitation, and modification—hemoglobin serves as an inspiration for research. The aim of the present review is to summarize recent investigations inspired by hemoglobin in the field of coordination chemistry. A brief outline of the coordination chemistry of the porphin system serves as an introduction.

1. Introduction: The Coordination Chemistry of the Porphin Ligand

Porphin [$H_2(P)$; *(1)*], which forms the parent substance of all porphyrins[1], contains four pyrrole rings linked into a macrocycle by methine bridges (see Fig. 1 and Table 1). Of the four inner nitrogens, two that are diagonally opposite each other carry labile protons that can be split off with bases. The resulting porphin dianion $(P)^{2-}$ has four pairs of free electrons pointing inward. Owing to its aromatic character, this ion forms a rigid, planar, closed, quadridentate chelate ligand system whose center can be occupied by metal ions of suitable size[2–8]. This process, called metalation, is shown in reaction (a) for the important Fe^{II} ion. This reaction, which is generally slow because of the rigidity of the porphin system, follows a complicated mechanism, since many bonds have to be broken and formed in its course[5, 6].

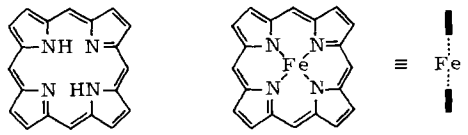
$$\underset{(1)}{H_2(P)} + Fe(OAc)_2 \underset{HCl}{\overset{HOAc,\ 110°C}{\rightleftharpoons}} \underset{(2)}{Fe(P)} + 2HOAc \qquad (a)$$

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The character of a rigid, closed chelate also explains the remarkable stability of porphyrin complexes. Thus, a formation constant of at least 10^{16} has been reported for a Zn^{II} porphin, related to the Fe^{II} porphin[5c]. Nevertheless, many metal ions can be abstracted from porphyrin complexes with the aid of strong acids. Thus, dilute hydrochloric acid is sufficient for such demetalation in the case of the Fe^{II} ion in the reverse of reaction (a).

The formation of the planar chelate Fe(P) *(2)*, an "inner complex salt" in the classical sense, by no means exhausts the possibilities offered by this system in coordination chemistry. In compound *(2)* the four nitrogens of the porphin ligand occupy the corners of a square, seen from the side in A (Figs. 1 and 2). This square in *(2)* can form the base of a pyramid B after the addition of a neutral donor ligand L, while after the addition of two donor molecules it can form the equatorial plane of a more or less tetragonally distorted octahedron C (Fig. 2). In the complexes B and C, formed in reaction (b), the donor molecules L act as "axial" ligands.

$$\underset{A}{Fe(P)} \overset{L}{\rightleftharpoons} \underset{B}{Fe(P)L} \overset{L}{\rightleftharpoons} \underset{C}{Fe(P)L_2} \qquad (b)$$



(1), $H_2(P)$ (2), Fe(P) A

Fig. 1. Formulas of porphin (1), the unsubstituted parent substance of all porphyrins, and of porphinatoiron (iron porphyrin) (2), the parent substance of all hemes.

Table 1. Abbreviations.

General symbols

M: central metal ion, L: axial donor ligand (neutral or anionoid), X: monovalent anion, $H_2(P)$: unsubstituted porphin (1)

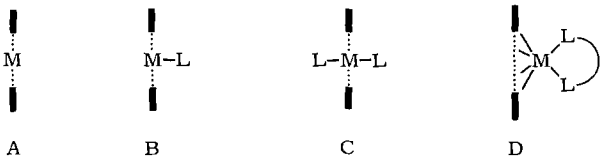
Special symbols

a) Hemoglobins
[Hb]: monomeric hemoglobin, [Mb]: myoglobin

b) Metal-free porphyrins (examples)
H_2(proto): protoporphyrin-IX [cf. (3a)],
H_2(meso-DME): mesoporphyrin-IX dimethyl ester [cf. (3d)],
H_2(TTP): *meso*-tetra(*p*-tolyl)porphyrin [cf. (6j)],
H_2(OEP): octaethylporphyrin [cf. (7a)];
H_2(Pc): phthalocyanine

c) Organic solvents or axial ligands or their corresponding acids
Py: pyridine, Hlm: imidazole, 1-MeIm: 1-methylimidazole, 2-MeIm: 2-methylimidazole, THF: tetrahydrofuran, DMF: dimethylformamide, MeCN: acetonitrile, PR_3: triorganylphosphane, HOAc: acetic acid, H(acac): 2,4-pentanedione (acetylacetone)

While the d^6 electron configuration of the Fe^{II} ion favors the formation of coordination type C, which is very common also with other central metal ions, the d_{z^2} orbital of metal ions with configurations d^7, d^8, and d^9, which is partly or fully occupied and lies in the axial direction, repels axial donor ligands, so that coordination type A predominates in the case of Co^{II}, Ni^{II}, Cu^{II}, and ions that are isoelectronic with these and are in the same groups of the periodic table[3-9].



A B C D

Fig. 2. The most important coordination types of metal porphyrins A: square [see (2)]; B: square pyramid; C: distorted octahedron (*trans* configuration); D: *cis* configuration in the addition of bidentate chelate ligands L⌒L (See Section 7.1).

As will be seen later, the possibility of adding on axial ligands is in fact essential for the biological function of iron porphyrins.

After *Richard Willstätter*'s[10] and *Hans Fischer*'s[1,11] significant contributions and the blossoming of organometallic chemistry after 1950, all metals and boron, silicon, germanium, and phosphorus have now been inserted into the porphyrin system[3-9]. Research in this field makes extensive use of physical and instrumental techniques[3,4], particularly X-ray structure analysis[12] and electron spin resonance spectroscopy[13]. As a result of this work, the coordination chemistry of metal porphyrins has grown into a separate field of coordination chemistry. This field is treated systematically in the appropriate sections of recent monographs and reviews[3-7].

The intensive work on porphyrins, illustrated by the publication of 44 articles in the Journal of the American Chemical Society in 1975 alone, stems from the great interest of chemists in heme proteins responsible for the transport of molecular oxygen in the body and for a wide variety of oxidation processes[14]. Yet this area itself is not so popular among chemists at present. The present review will treat hemoglobin as an inspiration for the chemistry of metal porphyrin complexes, without discussing the other heme proteins.

2. The Main Characteristics of Hemoglobin and Myoglobin

Human hemoglobin is a globular protein with a molecular weight of 64500, which gives the erythrocytes their red color (see Fig. 3) and enables them to transport oxygen[14-17]. The structure of hemoglobin with various axial ligands has been determined on single crystals by X-ray crystallography at a resolution of 2 Å[18]. Hemoglobin consists of four associated peptide chains (two α- and two β-chains), and its composition in the ligand-free state can be written as $[Fe(proto)G]_4$, where G is the apoenzyme globin and Fe(proto) is the coenzyme heme (3a), the latter being the iron(II) chelate of protoporphyrin IX (see Table 2).

Myoglobin has a molecular weight of 17000 and takes up oxygen in the muscle cells on its way to the mitochondria, thus accelerating its diffusion. In composition and structure it differs only slightly from one of the subunits of hemoglobin, specifically in the globin component, and can therefore be represented as [Fe(proto)G] (see above).

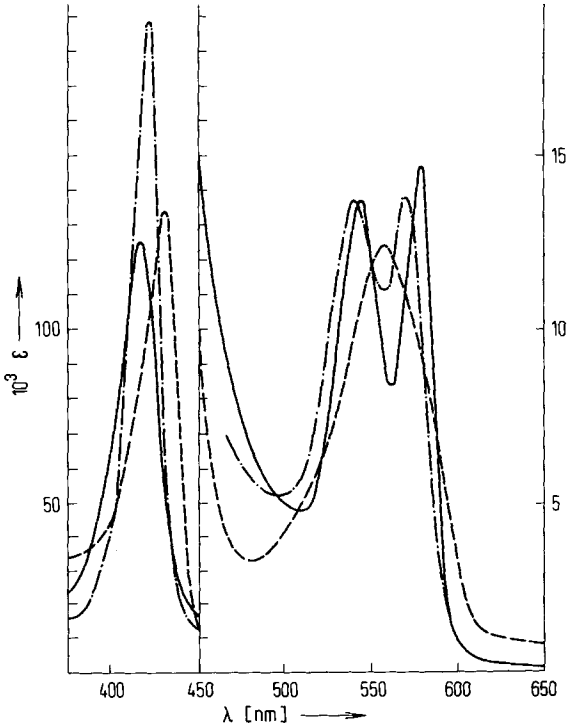
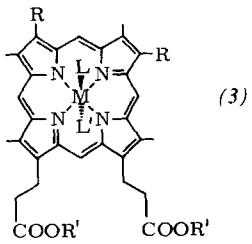


Fig. 3. Electronic absorption spectrum of oxyhemoglobin $[Hb{\cdot}O_2]_4$ (—), deoxyhemoglobin $[Hb]_4$ (– –), and carbonylhemoglobin $[Hb{\cdot}CO]_4$ (–·–) at pH 7 and 20°C (see Fig. 4). The longest-wavelength absorption maximum is called the "α band" (after [15]).



(3)

Table 2. Composition of metal porphyrins *(3)* of natural origin. (For abbreviations see Table 1.)

	M	L	L'	R	R'	Abbreviation
(3a)	Fe	—	—	$CH=CH_2$	H	Fe(proto)
(3b)	Fe	Cl	—	$CH=CH_2$	H	
(3c)	Fe	—	—	$CH=CH_2$	CH_3	Fe(proto-DME)
(3d)	Fe	—	—	C_2H_5	CH_3	Fe(meso-DME)
(3e)	Fe	—	—	H	CH_3	
(3f)	Fe	Hlm	Hlm	C_2H_5	H	
(3g)	Fe	—	—	$CH=CH_2$	C_2H_5	
(3h)	Co	Py	—	$CH=CH_2$	CH_3	
(3i)	Co	—	—	$CH=CH_2$	H	Co(proto)
(3j)	Yb	acac	—	C_2H_5	CH_3	

The term hemoglobin is also used nowadays in the broad sense as a generic name for all heme proteins that add on oxygen reversibly and transport it[16]. It is very confusing for outsiders that in physiological chemistry the abbreviations Hb and Mb are used for ligand-free hemoglobin and myoglobin, irrespective of their state of association, while there are also some hemoglobins that consist of a single peptide chain[16]. In contrast, the state of association will always be specified here, with the aid of the following abbreviations in square brackets:

human hemoglobin	$[Hb]_4 = [Fe(proto)G]_4$
hemoglobin subunit	$[Hb] = [Fe(proto)G]$
myoglobin	$[Mb] = [Fe(proto)G]$

Buse has given a protein chemist's account of the structure and function of hemoglobin, with special reference to the globin component[16]. Changes in the quaternary and tertiary structure (allosterism) are brought about by "allosteric effectors", low-molecular substances reacting with the protein. Allosterism is the basis of *e.g.* the Bohr effect (the pH-dependence of the overall oxygenation equilibrium shown [reaction (c)], with hydrogen ions as the effectors) and of the "cooperative" nature of the oxygen uptake, where the bound oxygen itself acts as an effector; a condition for this is an association of the subunits, *e.g.* to $[Hb]_4$. Contrary to expectation, there is much less driving force behind the first step of the oxygen uptake [reaction (d)] than behind the last step [reaction (e)], which ensures that the bound oxygen is released more easily in an oxygen-deficient medium a long way from the lungs. Finally, $[Hb]_4$ also takes care of about 60% of the reverse transport of CO_2 formed in cell respiration back to the lungs, but heme itself is not involved in this[14–16]. These effects cannot be discussed here in further detail.

$$[Hb]_4 + 4O_2 \rightleftarrows [Hb \cdot O_2]_4 \quad (c)$$

$$[Hb]_4 + O_2 \rightleftarrows \{[Hb]_3[Hb \cdot O_2]\} \quad (d)$$

$$\{[Hb \cdot O_2]_3[Hb]\} + O_2 \rightleftarrows [Hb \cdot O_2]_4 \quad (e)$$

The characteristics of hemoglobin that are considered essential by inorganic chemists will merely be outlined here, with what might seem ludicrous brevity, by representing the fundamental chemistry of a monomeric hemoglobin [Hb] in Fig. 4, this scheme referring both to a single subunit of human hemoglobin and to myoglobin [Mb].

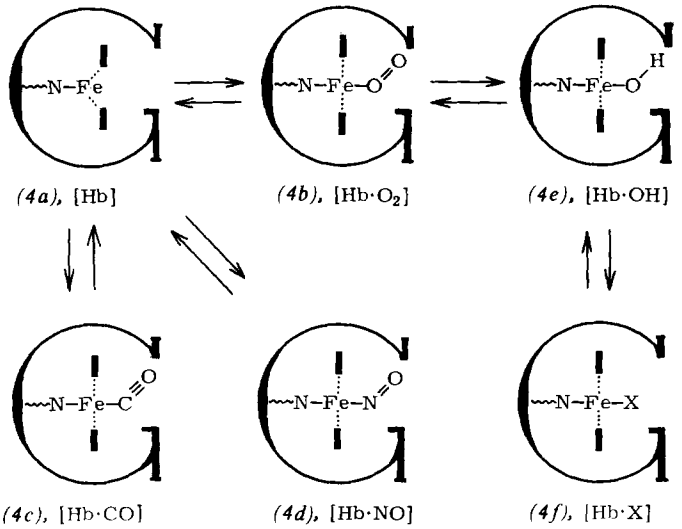


Fig. 4. Schematic representation of the essential chemistry of a hemoglobin unit [Hb] or myoglobin ([Mb] is then used instead of [Hb]). The letter G symbolizes the protein component, *i.e.* globin.

2.1. The Coordination Chemistry of Hemoglobin

In deoxyhemoglobin $[Hb]_4$ [cf. *(4a)*], the iron(II) ion is pentacoordinated (type B, Fig. 1), has an effective magnetic moment $\mu_{eff} = 5.4$ B.M.[19], and protrudes from the plane of the protoporphyrin[12,18] by about 50—60 pm. The heme component Fe(proto) *(3a)* is held in the "pocket" of the globin by van der Waals forces and the dative coordinate bond of the nitrogen atom shown in *(4a)*. This nitrogen belongs to the imidazole part of what is called the "proximal" histidine, which is not absolutely essential for fixing the heme in the globin but has a fundamental effect on the binding of ligands and probably also transmits the allosteric effects. "Distal" histidine, which is on the opposite side of the heme disk and is not shown in *(4a)*, cannot form a coordinate bond with the iron in heme because it is too far away; distal histidine is not essential for the binding of O_2, but seems to influence the entry of the ligand to the site of the bond formation[17,18].

Under physiological conditions (37 °C), $[Hb]_4$ reacts with molecular oxygen to give oxyhemoglobin $[Hb \cdot O_2]_4$ [cf. *(4b)*, while with carbon monoxide and nitric oxide it forms respectively carbonylhemoglobin $[Hb \cdot CO]_4$ [cf. *(4c)*] and nitrosylhemoglobin $[Hb \cdot NO]_4$ [cf. *(4d)*]. These reversible reactions cause characteristic changes in the visible spectra (Fig. 3). The association constants (K_{ass}) for the equilibria of the monomers have approximately the following relative magnitudes at comparable pH:

$$K_{ass}(4a) \rightleftarrows (4b) : K_{ass}(4a) \rightleftarrows (4c) : K_{ass}(4a) \rightleftarrows (4d)$$
$$= 1 : 4 \times 10^2 : 5 \times 10^{15} \text{ [15]}$$

The binding of CO or NO is therefore favored over the uptake of O_2. This is true for $[Hb]_4$, [Mb], and numerous

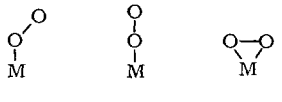
other heme proteins in the Fe^{II} form, and is the reason for the high toxicity of CO and NO. Since $[Hb \cdot CO]_4$ and $[Hb \cdot NO]_4$ dissociate much more slowly than $[Hb \cdot O_2]_4$[20], a chain-smoker can easily render 10% of his hemoglobin useless, owing to the carbon monoxide in the smoke[21]. The adducts $[Hb \cdot O_2]_4$ and $[Hb \cdot CO]_4$ are diamagnetic, while $[Hb]_4$ is not, and $[Hb \cdot NO]_4$ has an unpaired electron. The adducts are therefore in the low-spin state[19].

In the crystalline product, and to a small extent also under normal metabolic conditions in the blood, the oxygenation of $[Hb]_4$ to $[Hb \cdot O_2]_4$ is followed by oxidation to "methemoglobin" $[Hb \cdot OH]_4$ [(cf. *4e*)], which carries an OH on each Fe^{III} ion, and these OH groups can be protonated to give an aquo complex called "acid methemoglobin". With anions X^- (X = F, OAc, CN, N_3 etc.), $[Hb \cdot OH]_4$ gives a series of other ferrihemoglobins $[Hb \cdot X]_4$ [cf. *(4f)*], whose magnetic moments show a pure high-spin state for X = OH or F, an intermediate spin state for $X = N_3$, and a low-spin state for X = CN[19]. In the blood $[Hb \cdot OH]_4$ is constantly reduced again to $[Hb]_4$ by the "repair enzyme" methemoglobin-reductase[22]. When a dangerous level of $[Hb \cdot OH]_4$ has built up in the blood ("methemoglobinemia") under abnormal metabolic conditions, such as nitrite poisoning, $[Hb \cdot OH]_4$ can be converted back into $[Hb]_4$ by an intravenous injection of redox mediators such as methylene blue or toluidine blue[21]. Incidentally, sperm-whale metmyoglobin [Mb·OH] was the first protein whose crystal structure was determined by X-ray crystallography[23].

All the X-ray structure analyses[18] so far carried out on carbonylhemoglobins point to the presence of a bent Fe—CO unit with an Fe—C—O angle of about 145°. This is unusual in complexes and was first found by *Huber* in his work on the [Hb·CO] of the insect *Chironomus thummi*[24]. Otherwise a bent M—C—O unit has so far been found only in a single carbonyl complex, namely in $Mn_2(AsMe_2)(CO)_6C_5H_5$; the bent shape of a terminal Mn—CO group is attributed to steric hindrance due to neighboring groups[25]. Distal histidine in globin is likewise so oriented that it is in the way of a CO or CN ligand attached to the iron normally to the porphin plane; as a result, either the Fe—C—O unit is bent, as in *(4b)*, or the Fe—C—O axis is tilted from the perpendicular line of the porphin plane, but one cannot yet distinguish between these possibilities. On the other hand, bent diatomic or triatomic ligands, such as azide or hydroxide, fit better into the heme pocket[18]. Figure 4 shows these aspects and thus anticipates the results for $[Hb \cdot O_2]_4$ and $[Hb \cdot NO]_4$ to be discussed in Sections 2.2 and 4.

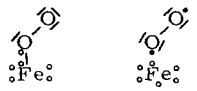
2.2. Nature of the Dioxygenyliron Group in Oxyhemoglobin

The structure and the distribution of the valence electrons in the dioxygenyliron unit in $[Hb \cdot O_2]_4$ or $[Mb \cdot O_2]$ have long been the subject of lively dispute[26–32], but this cannot be described here in detail. Unfortunately, it has not yet been possible to investigate the oxygenated forms by X-ray crystallography, because autoxidation to $[Hb \cdot OH]_4$ takes place during the lengthy process of data collection. In addition, the resolution of the structure analysis is not high enough to allow the determination of the space coordinates of the atoms next to iron with the accuracy that can be achieved with low-molecular complexes.



E F G

Therefore, in the case of a hemoglobin a decision is not yet possible between the three conceivable configurations of the FeO_2 unit in *(4b)*, namely the bent monodentate (E), the linear monodentate (F), or the bidentate arrangement (G). The bent structure E selected in Figure 4 was proposed by *Pauling* as long ago as 1949[26]. The form G, first discussed by *Griffith* in 1956[27], would be a π-complex of Fe^{II} or a peroxo complex of Fe^{IV}. There are no examples of the linear arrangement F in inorganic chemistry.



H K

The experiments described in Sections 5 and 6 show that the synthetic O_2 adducts of mononuclear iron(II) and cobalt(II) complexes have a bent structure of type E, so that the latter is also likely for *(4b)* itself. The adducts of O_2 (like O_2 itself) cannot be formulated unambiguously with valence signs. *Pauling* has suggested formula H[26], in which the iron is divalent, and which explains the apparent diamagnetism of the adduct. Formula K, introduced by *Weiss*[28], shows $[Fe(proto)O_2 \cdot G]$ as a neutral complex of the hyperoxide ion $[O_2]^-$. (In these formulas circles denote d electrons of iron, and points and lines denote valence electrons and valence electron pairs of dioxygen.) In the case of the structure K it is difficult to understand how the two unpaired electrons at the Fe^{III} ion and the terminal O atom can couple to form a diamagnetic system. The latest and very accurate measurements of the magnetic susceptibility show that $[Hb \cdot O_2]_4$ exhibits residual paramagnetism, whose temperature dependence between 3 and 30 K indicates an exchange interaction with a coupling constant of $J = 12$ K between the two ($S = {}^1/_2$) systems of an Fe^{3+} ion and an O_2^- ion[29].

Formula K gives a correct description of some other properties of *(4b)* and is therefore preferred at present. For example, the weak light absorption in the near infrared region at 900—1100 nm that is observed with *(4b)*, *(4e)*, and *(4f)* but not with *(4a)* and *(4c)* points to the presence of Fe^{III} in the first set of hemoglobin derivatives, *i.e.* in *(4b)*, *(4e)*, and *(4f)*. Furthermore, the IR spectrum of $[Hb \cdot O_2]_4$ and $[Mb \cdot O_2]$ exhibits an O—O stretching vibration with a frequency of about 1100 cm^{-1}, characteristic of the coordinated hyperoxide ion[30a–30c]. Besides, when Cl^- reacts with $[Hb \cdot O_2]_4$ in an aqueous solution, it is possible to detect the hyperoxide ion (or HO_2 radical) that is displaced from the heme in a nucleophilic substitution [reaction (f), with X = Cl]. This explains the continuous formation of methemoglobin in the blood mentioned above. The hyperoxide released here is also made harmless by enzymatic means. Other methemoglobins $[Hb \cdot X]_4$ [cf. *(4f)*, with $X = N_3$, SCN, OCN, F]

can also be prepared directly by an exchange of the anions according to reaction (f)[30d, 30e].

$$[Hb \cdot O_2]_4 + 4X^- \rightarrow [Hb \cdot X]_4 + 4O_2^- \quad (f)$$

According to recent quantum-mechanical *ab-initio* calculations, the Pauling configuration F has as much as 55 kcal·mol^{-1} less energy than the Griffith configuration G. However, the calculated electroneutrality of the O_2 ligand points to a predominance of the electron configuration H[31]. The calculations involve a great deal of simplification, NH_3 being used as the base *trans* to the O_2 molecule; this might not take sufficient account of the contribution of imidazole to the π-bonds, which has been observed experimentally[17].

The special effect of the porphyrin and the globin components can be seen by comparing the behavior of the Fe^{II} ion in hemoglobin and in water at pH 7: in hemoglobin there is a rapid reversible oxygenation, while in water there is an extremely slow and irreversible autoxidation (it is considerably faster in an alkaline medium). This difference is explained to some extent by the syntheses in which hemoglobin is modified and imitated and which will be discussed later, after the following notes concerning a reproduction of hemoglobin.

3. Copying: Remarks on the Total Synthesis of Hemoglobin

The total synthesis of a natural product, *i.e.* its nonenzymatic reproduction *in vitro*, does not explain its mode of operation but provides us with the necessary methods for modifying and imitating the molecule and thus for discovering the way it acts in nature. With the total synthesis of hemin *(3b)*, and thus also heme *(3a)*, *Hans Fischer* succeeded in 1929 in "copying" or reproducing the coenzyme of hemoglobin[33]. However, it is easier to extract hemin *(3b)* from blood than to synthesize it. For this, the blood is first treated with citrate to bind the calcium ions and to make it uncoagulable by suppressing fibrin formation. The erythrocytes are then made to burst (hemolysis) by producing an osmotic shock with water. After centrifuging, $[Hb \cdot OH]_4$ is obtained in the aqueous phase if the work is carried out in air. Globin is denatured and precipitated by the addition of strontium chloride and acetone[34]. The intact globin can be isolated with dilute hydrochloric acid in acetone at $-20°C$[15]. Hemin remains in solution in both cases. The process is as shown in reaction (g).

$$[Fe(proto)OH \cdot G] + HCl \underset{\text{reconstitution}}{\overset{\text{cleavage}}{\rightleftharpoons}} [Fe(proto)Cl] + G + H_2O \quad (g)$$

(4e) = [Hb·OH] *(3b)*

"Reconstitution", *i.e.* the recombination of heme *(3a)* and intact globin, was first achieved by *Hill* and *Holden* in 1926[35]. The overall process starts with the reversal of reaction (g), after which the resulting [Hb·OH] *(4e)* is reduced to complete [Hb] *(4a)* (see also Section 4). In a weakly alkaline medium (pH 7.2—8.0), the equilibrium in reaction (g) lies entirely to the left[15].

A total synthesis of the apoenzyme has not yet been described, but it seems feasible at the present state of protein research. The modification of globin is provided *in vivo* by the existence of many species-specific globin variants or mutants, which exhibit characteristic deletions or substitutions in their amino-acid sequence, leading to changes in the function of the molecule[15, 16, 36].

4. Variation I: Removal of the Globin Component—Coordination Chemistry of Heme and Hemin

The modification of the globin component on the basis of mutants occurring in nature belongs to the field of protein chemistry[16, 36]. Although this field is also instructive for inorganic chemists, we shall discuss here only one modification, namely the complete elimination of globin. Figure 5 shows the essential chemistry of heme *(3a)*, which exists preferentially as a complex $Fe(P)L_2$ [reaction (b)] when mixed with donor-solvent molecules L such as THF, DMF, and pyridine. These hemochromes (earlier called hemochromogens) *(5a)*, carbonylhemes *(5g)*, and hemins *(5f)* have long been known[1], whereas the other species were first isolated and characterized spectroscopically in the last decade.

Owing to the strongly polar carboxyl groups and the labile vinyl groups, it is not practical to use protoheme *(3a)*, which can be obtained from the blood *via* hemin *(3b)*. It is better to convert it into the dimethyl ester [Fe(proto-DME)] *(3c)*

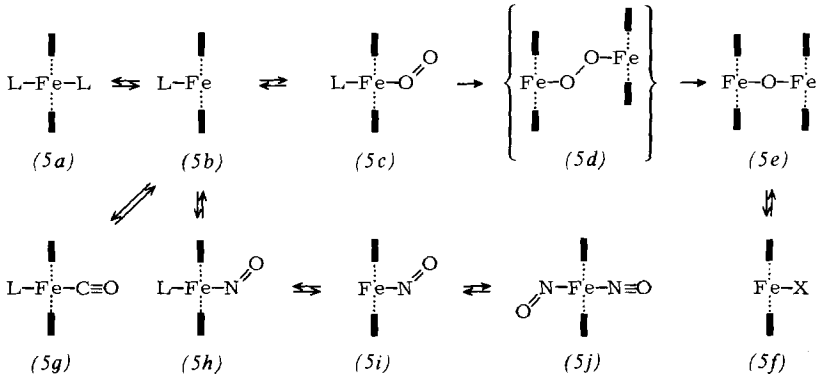
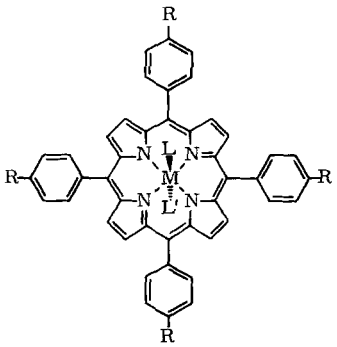


Fig. 5. Schematic representation of the essential chemistry of the heme Fe(P), especially iron(II) protoporphyrin Fe(proto) *(3a)* or the corresponding derivative of tetraphenylporphyrin Fe(TTP) *(6a)*, or octaethylporphyrin Fe(OEP) *(7a)*. The coordination types are designated as *(5a)*—*(5j)*.

or to hydrogenate it further to the mesoporphyrin derivative [Fe(meso-DME)] *(3d)*. The labile vinyl groups are often eliminated completely, and the dimethyl ester of deuteroporphyrin-IX *(3e)* is used for further work. To avoid these steps and the asymmetric arrangement of substituents which leads to complicated spectra, one can use either cheap tetraphenylporphyrin [H_2(TPP)], which can be prepared from pyrrole and benzaldehyde in a single step[3,4,37], or octaethylporphyrin [H_2(OEP)], which is expensive but is the most convenient to use. The incorporation of iron in reaction (a) or with the aid of iron(II) 2,4-pentanedionate[9,38] gives the heme Fe(TPP) *(6a)* or Fe(OEP) *(7a)* (see Tables 3 and 4). In solution, all hemes are very sensitive to air and are readily autoxidized to hemins *(5f)*, which are usually isolated after the insertion of iron. A very convenient way to incorporate the iron, described by *Hans Fischer*[1], is to use $FeCl_3$ in boiling glacial acetic acid and sodium acetate. The porphin is dissolved out of an extraction thimble in the course of about a day, and the chlorohemin Fe(P)Cl [*(5f)* with X = Cl] crystallizes on cooling.



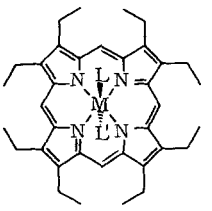
(6)

Table 3. Examples of metal tetraarylporphyrins *(6)*. (For abbreviations see Table 1.)

	M	R	L	L'
(6a)	Fe	H	—	—
(6b)	Fe	H	CO	Py
(6c)	Fe	H	NO	—
(6d)	Fe	H	NO	1-MeIm
(6e)	Fe	H	2-MeIm	—
(6f)	Co	OMe	Py	—
(6g)	Co	H	—	—
(6h)	Mn	H	Py	—
(6i)	Cr	H	Py	—
(6j)	Os	Me	—	—
(6k)	Os	Me	N_2	THF
(6l)	Ru	H	CO	Py

More care is needed for the introduction of iron into the much more labile H_2(proto), *i.e.* into the iron-free *(3a)*. For this, a solution of H_2(proto) in pyridine is combined with a solution of $(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$ in maximum-purity glacial acetic acid in the absence of air and the mixture is heated to 80°C for 1 h. The resulting Fe(proto) *(3a)* is oxidized by air in the cold and is converted into hemin *(3b)* by treatment with HCl[2,3,34b].

After treatment with reducing agents, such as sodium dithionite, hydrazine, chromium(II) 2,4-pentanedionate, $NaBH_4$, or palladium/calcium hydride, the required neutral ligands L, such as pyridine or 1-methylimidazole (1-MeIm), are added to the hemin solutions, the solvent is evaporated, and the solid hemochromes *(5a)* are isolated[1-4]. These hemochromes react with carbon monoxide and nitric oxide, giving the similarly crystallizable carbonylhemes *(5g)*[1-4,39] and



(7)

Table 4. Composition of metal octaethylporphyrins M(OEP)LL' *(7)*. (For the abbreviations see Table 1.)

	M	L	L'		M	L	L'
(7a)	Fe	—	—	*(7j)*	Os	OMe	OMe
(7b)	Fe	CO	Py	*(7k)*	Os	N_2	DMF
(7c)	Ru	CO	Py	*(7l)*	Os	NO	NO
(7d)	Os	CO	Py	*(7m)*	Os	NO	OMe
(7e)	Ti	O	—	*(7n)*	Ru	Py	Py
(7f)	Os	O	O	*(7p)*	Ru	NO	OMe
(7g)	Os	N_2	THF	*(7q)*	Fe	Py	Py
(7h)	Os	Py	Py	*(7r)*	Ru	MeCN	MeCN
(7i)	Os [a]	Py	Py	*(7s)*	Os	MeCN	MeCN

[a] Cationic Os^{III} complex.

nitrosylhemes *(5h)*[40-43], respectively. In nitrosylhemes *(5h)*, only the ligand L *trans* to the nitrosyl group can be easily split off, giving *(5i)*. This has recently also been observed with $[Hb \cdot NO]_4$[40b,40c]. X-Ray crystallographic analysis has elucidated the structures of the carbonylheme Fe(TPP)CO(Py) *(6b)*[39g] and nitrosylhemes Fe(TPP)NO *(6c)* and Fe(TPP)NO(1-MeIm) *(6d)*[41]. Unlike $[Hb \cdot CO]_4$, the Fe—C—O group is linear and oriented normally to the porphin plane. According to *Scheidt*, the Fe—N—O unit is bent, the Fe—N—O angle being 149° in *(6c)*[41b] and 140° in *(6d)*[41c]. These angles agree with the assumption that nitric oxide is basically a neutral ligand here. The donor action of the imidazole system in the *trans* position in *(6d)* imparts a partial anionoid character to the NO, as can be seen from the widening of the angle on going from *(6c)* to *(6d)*. Since Fe(proto-DME)NO(1-MeIm) (dissolved in 1-methylimidazole, $\nu_{NO} = 1618\,cm^{-1}$) and $[Hb \cdot NO]_4$ ($\nu_{NO} = 1615\,cm^{-1}$) exhibit virtually the same NO frequency, it can be assumed that the FeNO unit has a bent configuration in $[Hb \cdot NO]_4$ as well[40b].

The complexes of the type *(5a)*, *(5g)*, and *(5i)*, which are fairly stable in the solid state in air, readily undergo autoxidation in solution, particularly in the absence of an excess of ligands. As expected, *(5a)* and *(5g)* are diamagnetic, while *(5i)* has an unpaired electron and takes on a further NO reversibly at −196°C to form the dinitrosyl complex *(5j)*[42].

Like the reversible reactions of $[Hb]_4$, the conversions of globin-free hemes start from a pentacoordinate species of type B, such as *(5b)*[43], these compounds being formed mainly by the dissociation of the hexacoordinate complexes *(5a)*. When a sterically hindered axial ligand like 2-methylimidazole (2-MeIm) is used, *(5b)* can also be prepared in the crystalline state. Thus, *Collman et al.* have isolated Fe(TPP)(2-MeIm) *(6e)*[44], and even managed to crystallize the bare heme

Fe(TPP) *(6a)* with the established square geometry A[45]. However, *Hans Fischer et al.*[1] and *Caughey*[46] had prepared such bare hemes before; for example, Fe(proto-DME) *(3c)* or Fe(OEP) *(7a)* are also formed when the hemochromes *(5a)* are heated in high vacuum[40b,46].

It has only recently been found that the reversible oxygenation is not restricted to $[Hb]_4$ and [Mb]. Thus, the existence of oxygen adducts *(5c)*, formed analogously to *(4b)* (see Figs. 3 and 4), has been demonstrated for a number of hemes, such as *(3c)*[47], *(3d)*[48], and *(6a)*[39c], with the aid of low-temperature absorption spectroscopy in solution at −50°C. When heated to room temperature, these adducts undergo autoxidation to the binuclear iron(III) complexes *(5e)* at a rate that depends on the solvent used[46a]. It is generally assumed that the autoxidation starts with an attack of a second heme *(5b)* on the dioxygen complex *(5c)*, as a result of which a μ-peroxo complex *(5d)* is formed. This might then change into *(5e)* by symmetrical cleavage to (P)Fe=O and by the further reaction of this iron(IV) species with excess iron(II) porphyrin *(5b)*. In this series of reactions *(5b)* → *(5c)* → *(5d)* → *(5e)*, the axial ligands L are lost. The NMR spectroscopic monitoring of the autoxidation of Fe(P) [P = *meso*-tetra(*o*-tolyl)porphyrin] into (P)Fe—O—Fe(P) in toluene at −30°C does indeed indicate an intermediate, which is probably the μ-peroxo complex *(5d)*[49].

The end products of the autoxidation, the μ-oxo-bis(iron(III)-porphyrins) *(5e)*, are identical with hematins, to which the formula Fe(P)OH [*(5f)*, with X = OH] was previously ascribed. The approximately linear Fe—O—Fe bridges present in them according to crystal structure analyses[12,50] cause an antiferromagnetic interaction between the two Fe^{III} ions, which leads to magnetic moments that are abnormally low at room temperature and disappear altogether at −250°C[50,51]. Unlike $[Hb \cdot OH]_4$ [cf. *(4e)*], mononuclear globin-free hydroxoiron(III)porphyrins *(5f)*, with X = OH, do not exist as isolable substances. Attempts to obtain them by the alkaline hydrolysis of a hemin Fe(P)X *(5f)* are invariably followed by condensation to *(5e)* according to reaction (h) (but see Section 8).

$$\underset{(5f)}{2\,Fe(P)X} \underset{2\,HX}{\overset{2\,OH}{\rightleftharpoons}} 2\,Fe(P)OH \underset{+\,H_2O}{\overset{-\,H_2O}{\rightleftharpoons}} \underset{(5e)}{(P)Fe{-}O{-}Fe(P)} \qquad (h)$$

The binuclear nature of hematins would have certainly been noticed before if the elementary analysis had been extended to oxygen[9,38].

The last remarkable phenomenon to be mentioned here is the reverse reaction of the hemin type *(5f)* with electrochemically produced hyperoxide ions to form the dioxygen adduct *(5c)* in reaction (i), observed by *Hill* in DMF at −50°C[52]. This reaction is the reversal of the formation of methemoglobin in reaction (f) and is a further indication of the hyperoxide character of the bound O_2 molecule.

$$Fe(proto\text{-}DME)OClO_3 + O_2^- + DMF \rightarrow Fe(proto\text{-}DME)DMF \cdot O_2 + ClO_4^- \qquad (i)$$

It appears from all this that the iron ion in hemoglobin has, pictorially expressed, two "garments": under the globin "cloak", it wears the red "gown" of porphyrin.

Each plays a part in affecting the reactivity of the iron ion. First of all, the inner envelope ensures that the formation of insoluble polynuclear hydroxo and μ-oxo-iron(III) complexes, which is dangerous in the biological medium (aqueous system, pH ≈ 7, air) is restricted to the formation of binuclear μ-oxo complexes *(5e)*, which readily decompose according to reaction (h). The contribution of the porphyrin ligand to this is an acceleration of the exchange of the axial ligands on the Fe^{III} ion. As a result, the solvent exchange in DMF is faster with the complex ion $[Fe(TPP)(DMF)_2]^+$, which probably exists in it, than with the cation $[Fe(DMF)_6]^{3+}$[53]. A labilization of the axial ligands is also assumed for the Fe^{II} porphyrin system, because Cr^{III}, Co^{III}, and Ru^{II} porphyrins also have rates of substitution that are not normally expected for inert complexes of these ions with d^3 or d^6 configuration[54,55]. This labilization, which was first noted by *Fleischer*[54] and is very important for the rapid establishment of the oxygenation equilibrium (c), is attributed to the additional π-acceptor function of the porphinate ligand, which is brought about by the delocalized π-electron system and which becomes effective when the central metal ions possess occupied d_{xz} or d_{yz} orbitals, from which some of the electron density can diffuse to the unoccupied e_g (π*) molecular orbitals of the porphyrin system[2-4]. This removes the degeneracy of the d_{xz}, d_{yz}, and d_{xy} orbitals that leads to the inert character of systems in the d^3 or d^6 configuration. This type of information comes mainly from studying porphyrin complexes with central metals other than iron (see Sections 6 and 7).

However, globin, which forms the second envelope of hemoglobin, constitutes an effective system only in the blood. Porphyrin has conferred the above-mentioned reaction advantages on the iron ion, but—owing to its own hydrophobic nature—has not made this ion water-soluble at all; this can only be done by combination with globin, which has a hydrophilic periphery, making dissolution in water possible. On the other hand, the hydrophobic inside space of globin shelters heme properly. The low dielectric constant of this inner medium makes it difficult for the dioxygen adduct to dissociate into a hyperoxide ion and methemoglobin in reaction (f). However, this shell has another, and quite fundamental, effect in that it inhibits the attack of a second heme on the already oxygenated heme and thus also the step *(5c)*→*(5d)* (Fig. 5), which starts the irreversible autoxidation of heme in a nonpolar medium. The longer life of oxyhemoglobin *(4b)* in comparison with dioxygenylheme *(5c)* is thus due to an inhibition of the subsequent reactions of oxygenation, which is confirmed by the investigations described in Section 5.

As mentioned before, globin is also responsible for the cooperative effects. Besides, it is worth mentioning that the oxidation potential of the iron(II) ion in [Mb] (0.05 V) is very close to zero, and thus the driving force behind the autoxidation to [Mb·OH] is relatively small[15,56]. Finally, globin provides as an axial ligand an imidazole group that can act simultaneously as a σ-donor, π-donor, and π-acceptor, and thus it facilitates the addition of dioxygen, and also carbon monoxide, in the *trans* position. Whereas the σ-donor/π-acceptor effect is well known[17,56b], the important π-donor effect has only emerged from recent analyses of the *cis*- and *trans* effects, which were carried out on metal porphyrins but which will not be discussed here[39c,57].

5. Imitation of Hemoglobin: Iron-containing Myoglobin Models

A complete simulation of all the functions of hemoglobin by a given metal complex calls for numerous characteristics, of which it suffices to mention the following:

1) The formation of an O_2 adduct *(5c)* from *(5b)* should be reversible.

2) The adduct *(5c)* should be stable in a liquid phase, *i.e.* in solution, at 37°C, so that it can be transported in a pipeline system of conduits.

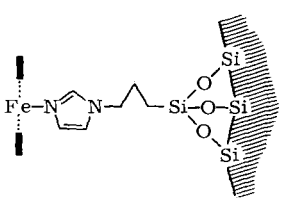
3) The adduct *(5c)* should be incorporated in a water-soluble protein, for only then can blood serve as a transport medium, and the adduct would not be excreted by the kidneys[14a]. (It is not taken into account here that $[Hb \cdot O_2]_4$ is in turn incorporated in the erythrocytes, which also impedes excretion.)

4) It should be possible to adjust the affinity of *(5b)* for oxygen to the prevailing physiological and biological conditions (different O_2 partial pressures), which means that it should be possible to control the system through allosterism.

The first requirement is fulfilled even by solid model substances, while the second calls for a soluble species. The third and fourth requirements are of a typically physiological nature. The designation "myoglobin models" is intended to indicate that one cannot expect a simulation of the cooperative effects.

5.1. The Concept of Immobilization

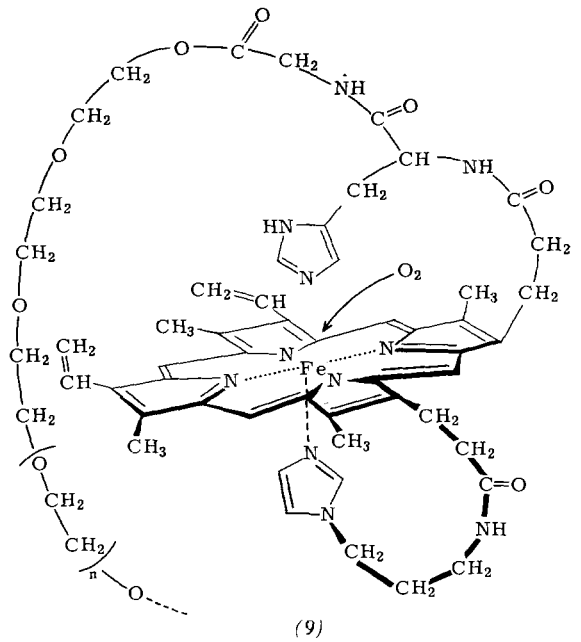
The first attempts to imitate hemoglobin by the use of iron porphyrins date back about 20 years. Thus, *Corwin* and *Bruck*[58a] studied the oxygen uptake of the solid imidazole-hemochrome Fe(meso)(HIm)$_2$ *(3f)* at room temperature. At 60—65°C the adduct suffered a loss of weight in vacuum, corresponding to the binding of 1 mol of O_2 per mol of hemochrome. This indicated a reversibility of the O_2 addition. Using carbon monoxide, 1-phenethylimidazole, the diethyl ester of Fe(proto) *(3g)*, and polystyrene, *Wang*[58b] obtained a carbonylheme of type *(5g)* embedded in polystyrene. Elimination of the CO with an inert gas left behind a heme assumed to be of type *(5b)*, which was capable of taking up O_2 reversibly, as was indicated by the visible spectrum typical of *(5c)* and *(5b)* in the presence and the absence of O_2, respectively. Both these studies were based on the concept of "immobilization" of the heme. When in the solid state or bound to a matrix, the heme molecules are not sufficiently mobile to form the μ-peroxo complex *(5d)*.



(8)

Returning to the concept of immobilizing heme, *Basolo et al.*[59] have recently obtained a heme with the partial formula *(8)*, fixed in a silica gel matrix. For this purpose, 3-chloropropyl groups were first introduced on the silica gel surface with 3-chloropropyltrimethoxysilane, and the chlorine in these 3-chloropropyl groups was then replaced by the imidazole group. This was followed by the addition of Fe(TPP) *(6a)* as the heme component, and the resulting heme, fixed on the silica gel, was finally brought into the active form of type *(5b)* denoted by *(8)* by drying at 250°C in high vacuum. System *(8)* is capable of chemisorption of molecular oxygen that is weak at room temperature, strong at −78°C, and irreversible at −127°C. No autoxidation to the μ-oxo complex of type *(5e)* was observed. Carbon monoxide is also taken up at room temperature and is only given off again at 160°C in a current of helium.

It has also been possible to immobilize heme in solution by fixing Fe(TPP) *(6a)* as the heme component on partially quaternized poly(4-vinylpyridine)[60a]. The heme-polymer adduct thus obtained was stable to oxidation in a mixture of DMF and water, but it absorbed oxygen, which could be displaced from it by CO as in the case of *(4b)* and *(5c)*. However, no reversible binding of O_2 was observed, and the identification of the presumed adduct of type *(5c)* is incomplete.



(9)

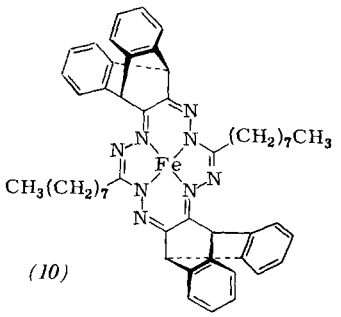
Much more sensational is *Bayer* and *Holzbach*'s publication about synthetic heme polymers, describing *e.g.* the preparation of the macromolecule *(9)*[60b]. In *(9)*, the heme carries not carboxyl groups as in *(3a)* but amide functions, coming from 3-(1-imidazolyl)propylamine and terminal histidine groups, two of which complete a chain of polyethylene glycol bis(glycine ester) with an amide-type bond. Besides the immobilization of heme in the polymer coil, other concepts were also involved here, which have already been worked out on low-molecular myoglobin models, such as the fixing of an imidazole residue on the heme to simulate the proximal histidine [cf. *(11)*]; the distal histidine has also been simulated (see Section 5.2).

In fact, the macromolecule *(9)* resembles $[Hb]_4$ in many respects: It can go through a number of oxygenation cycles in aqueous solution and gives an S-shaped oxygen sorption isotherm. In view of the binuclear nature of this heme complex, this second effect, which points to a cooperative character,

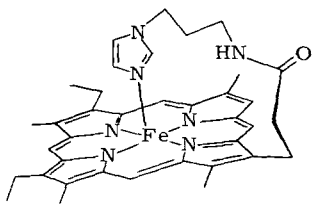
is not entirely unreasonable [formula *(9)* shows only one heme terminus of the polymer chain completed by two heme units], but the visible spectra of *(9)* in various ligand states indicate that the species are not uniform, and further experimental details need to be reported.

5.2. Monomolecular Myoglobin Models

The model substances described in Section 5.1 have the short-coming that the heme envelope in them is by no means "tailor-made". Therefore, we cannot expect the heme package to have a long life in these systems. Another idea is to link heme firmly to its envelope by introducing steric hindrance on heme itself with the aid of bulky substituents strongly bonded through C—C bonds. In 1973—75 numerous authors competed to be the first to prepare such monomolecular soluble myoglobin models.



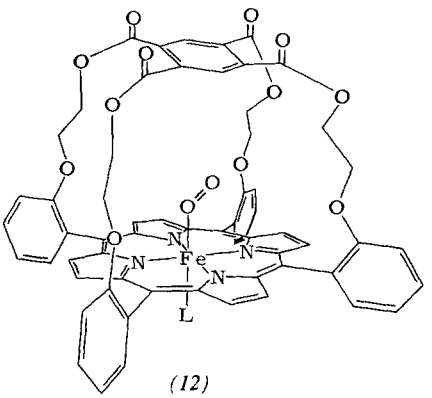
(10)



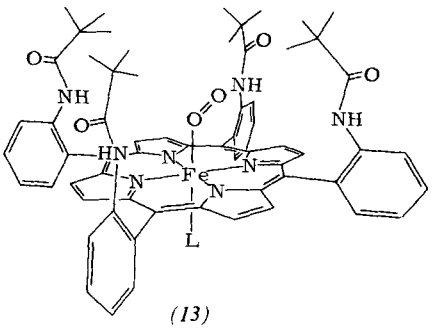
(11)

Baldwin and *Huff*[61] described in 1973 the first synthetic iron(II) complex *(10)*, which is a rigid macrocyclic chelate similar to heme but can be oxygenated reversibly only at low temperatures. *Chang* and *Traylor*[62] were the first to show with the peripherally modified heme *(11)* that globin-free hemes can also be reversibly oxygenated at low temperatures. The coordination type B is stabilized in *(11)* on account of the chelate effect, because the imidazole ligand is firmly connected with one of the porphyrin side chains. However, the stabilization of type B, *i.e.* of the complex *(5b)* analogous to deoxyhemoglobin *(4a)*, is not necessary for reversible oxygenation, since the usual hemes *(3c)*, *(3d)*, and *(6a)* also give the reaction *(5b)* ⇄ *(5c)* at −50 °C[39c, 47, 48] (see Section 4). Nevertheless, heme *(11)* and related systems are still useful for studying the reaction mechanism and the bonding of small molecules in detail[63], though this will not be discussed here.

The first systems that can be reversibly oxygenated at room temperature were prepared by *Baldwin*[64], *Collman*[65–67] and their associates; these are *Baldwin*'s "capped heme" *(12)* (crown heme[6]) and *Collman*'s "picket fence heme" *(13)*. Both of these have been given the formula *(5c)*, which is analogous to *(4b)*. The globin pocket is in these compounds to some extent fused with the porphyrin system. One of the sides of the porphyrin disk is covered by bulky substituents in such a way that no irreversible autoxidation can take place as long as the other side is occupied by axial ligands, such as 1-methylimidazole, that favor reversible oxygenation. It has thus been possible to carry out "several" cycles of reversible oxygenation at 25 °C with *(12)* and *(13)* [at least three with *(12)*] without any notable irreversible oxidation taking place. After the addition, the oxygen was cleaved off from *(12)* by freezing and the application of vacuum, and from *(13)* by flushing with nitrogen. The dioxygenyl complexes *(12)* and *(13)* have even been isolated as pure solid substances.



(12)



(13)

For *(13)*, crystal structure analysis has indicated structure E, *i.e.* a monodentate, bent dioxygen chain bound to the iron atom[66], although it should be mentioned that this analysis did not have the accuracy attainable nowadays, owing to the mediocre quality of the crystals and the disordered arrangement of the bound oxygen molecule. After initial difficulties, the typical IR bands of the FeO_2 system have been detected (at 1159 cm^{-1}), and the magnetic data and the Mössbauer spectra of *(13)* agree with those of $[Hb \cdot O_2]_4$, so that the Pauling structure E is also valid for $[Hb \cdot O_2]_4$[66, 67].

The sterically hindered porphyrin ligands in *(12)* and *(13)* were prepared by conventional methods of organic chemistry[37]. The key compound forming *(12)* was the pyromellitate tetrakis[2-(2-formylphenoxy)ethyl]-1,2,4,5-benzene tetracarboxylate, which condensed with pyrrole to give the *meso*-substituted porphyrin that gave the heme component in *(12)* after the incorporation of iron[64]. The decisive step in the synthesis of *(13)* was the chromatographic separation of the atropo-isomers of α,β,γ,δ-tetrakis(2-aminophenyl)porphyrin. The isomer that had all the amino groups on the same side of the porphyrin disk was acylated with pivaloyl chloride and converted into the heme component *(13)* by the incorporation of iron[65, 66].

However, *(12)* and *(13)* have a limited lifetime in solution, because the detachment of the imidazole ligand can start an autoxidation and μ-oxo complex formation at the lower, unprotected side of heme. In hemoglobins, however, the axial ligand *trans* to the O_2 molecule, the proximal histidine, is also supplied by the enveloping globin [*(4b)*, *(4c)*]. The

number of cycles can be raised to 200 by making use of immobilization, *i.e.* by the reversible formation of *(13)* in the solid state. The thermodynamic data for this reaction show a remarkable agreement with those of myoglobin[67b].

The use of a rather aprotic medium is important for a long life of the dioxygen complex, as can be seen from the fact that, when the pivaloyl amide groups in *(13)* are replaced by the more strongly acidic *p*-toluenesulfonamide groups, the corresponding O_2 adduct cannot be detected[66]. The presence of unsubstituted imidazole in the solution has the same effect[48, 64].

The synthesis of the sterically hindered hemes *(12)* and *(13)* has stimulated many other laboratories engaged in porphyrin synthesis to prepare further porphyrins with bulky side chains or side chains bonded like cyclophane[68], but these variants have not yet supplied coordination chemists with any fundamentally new results.

None of the models discussed here fulfils all the requirements for a perfect imitation of hemoglobin. They possess only the first two necessary characteristics, *i.e.* reversible adduct formation and transportability. In contrast, the well characterized model substances *(12)* and *(13)* are not soluble in water and have a low molecular weight, so that they would be removed from the blood by renal ultrafiltration and are therefore unsuitable as blood substitutes, not to mention the allosteric effects, which must be absent in the case of a monomolecular model. Nevertheless, the synthesis and structure analysis of such model substances are highly instructive and fruitful for hemoglobin research and for preparative coordination chemistry.

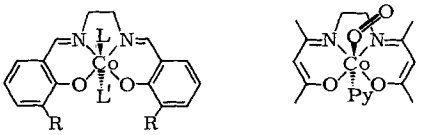
6. Variation II: Coboglobin and Other Metalloglobins

In the description of work aimed at imitating the biological function of hemoglobin in the previous section we deliberately ignored the publications dealing with the reversible oxygenation of metal complexes containing neither iron nor porphyrin ligands. The aim was to adhere closely to the original example, although basically any reversibly oxygenable metal complex is an imitation of hemoglobin at the simplest level. The whole field of reversible oxygenation of metal complexes is very large and is covered comprehensively in many reviews, some of them giving even the more recent results[56, 69–71], so that we shall deal here only with data of direct relevance to our topic.

We shall examine in this section the possibility of varying the central metal in hemoglobin, *i.e.* examine which other metals can be incorporated in hemoglobin instead of iron without suppressing its main biological function, *viz.* the transport of oxygen. According to *Vaska*, only certain complexes of manganese, copper and all Group 8 metals react with molecular oxygen[71]. Besides iron, only cobalt (which lies next to iron and has one more d electron) forms complexes that bind O_2 in a demonstrably monodentate manner. In the case of manganese this arrangement is not yet certain. All the others hold the O_2 in a bidentate manner as in G and can, in a simplified way, be regarded as peroxo complexes. There is no question here of an imitation of $[Hb \cdot O_2]$, because of their structural and electronic difference from it, even if they can take up oxygen in a reversible manner.

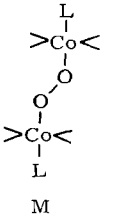
6.1. Development of Coboglobin

A cobalt(II) chelate—salcomin *(14a)*, first prepared by *Pfeiffer* in 1933[72]—was incidentally the first reversibly oxygenable metal complex known[73]. However, a complex does not have to be a planar chelate to be capable of reversible oxygenation, as has since been proved by many investigations[70]. Most adducts are diamagnetic μ-peroxodicobalt(III) complexes of type M, which are much more stable than the corresponding iron complexes *(5d)*. *Calderazzo*[74] first described the preparation of a mononuclear 1:1 chelate complex *(14b)* in 1969. *Basolo* and *Hoffman*[69] studied at the same time the formation of the analogous complex *(15)* at 0°C in DMF. The ESR spectra of *(15)* and of numerous similar



	R	L	L'
(14a)	H	–	–
(14b)	OMe	O_2	Py

(15)



M

compounds have been ascribed to the Co^{III} hyperoxide species having structure E. This has been proved correct by the determination of the crystal structure of *(15)*[75] and of a large number of corresponding adducts[69–71].

It was now an obvious step to the porphyrin system, and *Walker*[76] and the teams of *James* and *Ibers*[77] discovered almost simultaneously, by electronic absorption spectroscopy and ESR spectroscopy, the reaction (j) with various cobalt(II) porphyrins Co(P)L such as *(3h)* and *(6f)*, proceeding to a small extent at room temperature and readily at temperatures below −20°C.

$$Co(P)L + O_2 \rightleftarrows Co(P)L(O_2) \qquad (j)$$

In the presence of an excess of base, there is autoxidation to the cobalt(III) species in this case as well. These experiments established the analogy with iron-porphyrin chemistry (see Sections 2, 4, and 5), and the results obtained with the two systems mutually confirmed each other.

This analogy between iron and cobalt received its ultimate demonstration in the work of *Hoffman et al.*, who "reconstituted" coboglobins from Co(proto) *(3j)* and globins by methods described in connection with the heme Fe(proto) *(3a)* (see Section 3). These cobalt analogs of myoglobin [CoMb] or hemoglobin $[CoHb]_4$ show an amazing similarity to [Mb] or $[Hb]_4$. Thus, both these analogs take up oxygen reversibly at room temperature! However, the formation constant of the "original", $[Mb \cdot O_2]$, is almost a hundred times higher than that of $[CoMb \cdot O_2]$. Furthermore, $[CoHb]_4$ too exhibits allosteric effects such as the Bohr effect (see Section 2) and the cooperative behavior in the O_2 uptake, although to a smaller extent[78]. The cobalt analog of *(13)* has also been found in the meantime; the equilibrium mixture contains about 25% of this adduct besides the starting material (type B) in toluene at room temperature[79].

Although coboglobin has a much lower affinity to oxygen, it surpasses its "original" in one respect of ecological interest: it does not take up carbon monoxide. Therefore, living organisms that have coboglobin instead of hemoglobin should be capable of existing in an atmosphere containing more CO, since the latter would be only physically dissolved in their blood. Besides, Co^{II} porphyrins also give only a limited reaction with CO. *Wayland et al.* have shown that Co(TPP) *(6g)* takes up CO in reaction (k) only at very low temperatures and only in the absence of a nitrogen or phosphorus donor[80]. Since coboglobin contains a nitrogen donor in the form of the proximal histidine, it is inert to carbon monoxide.

$$Co(TPP) + CO \rightleftharpoons Co(TPP)CO \qquad (k)$$

In contrast, Co(TPP) and coboglobin add on nitric oxide to the same extent[78,80]. The additional electron in the d_{z^2} orbital of the Co^{II} ion evidently repels CO, but pairs off with an unpaired electron of the radical-molecule O_2 or NO; Co(TPP)NO is diamagnetic, contains a bent Co—N—O unit, and is isoelectronic with the corresponding FeO_2 system[81].

6.2. Other Metalloglobins

As mentioned at the beginning of this section, according to *Vaska* not only Co^{II} but also Mn^{II} might function as a central metal ion in place of the Fe^{II} ion in hemoglobin. In fact, the reversible oxygenation of Mn(TPP)Py *(6h)* in reaction (l) has recently been detected at low temperatures[82]. On the other hand, Cr(TPP)Py *(6j)* adds on oxygen irreversibly, presumably with the formation of a hyperoxide complex[83].

$$Mn(TPP)Py + O_2 \rightleftarrows Mn(TPP)O_2 + Py \qquad (l)$$

Since the relatively large high-spin Mn^{II} ion in Mn(TPP) is not coplanar with the porphyrin system[82c] and reaction (l) follows the stoichiometry given, it is concluded that pyridine is replaced by O_2 in a frontal attack. Accordingly, the "manganoglobins" $[MnHb]_4$ and [Mn·Mb] prepared by several teams cannot add on oxygen, since in the reconstituted system the O_2 would have to displace the relatively immobile proximal histidine[84–86]. However, manganoglobins are still interesting: $[MnHb]_4$ exhibits a Bohr effect and, when binding NO, the allosteric cooperative effects known for $[Hb]_4$[86]. Unlike O_2 and CO, the NO[87,88] can therefore be bound, because only the particularly strong π acceptor NO can effect a transition of the Mn^{II} ion into the low-spin state during the addition. In this state the Mn^{II} ion is smaller and capable of assuming the octahedral configuration C, as for example in Mn(TPP)NO(L) (L = 4-methylpiperidine)[87], which must also be present in $[MnHb \cdot NO]_4$. The constitution of $Mn(TPP)O_2$ formed in reaction (l) is still unclear. *Basolo* suspects a peroxo complex of Mn^{IV} (structure G)[82b], while *Lever*[89] assumes the formula of a hyperoxomanganese(III) complex (structure E) for his O_2 adduct obtained from manganese(II)-phthalocyanine Mn(Pc).

The metalloglobins obtained by "reconstitution" from Cu(proto) or Zn(proto)[84,90] are unsuitable as O_2 carriers, since Cu^{II} and Zn^{II} normally cannot donate any more electrons. In addition, Cu^{II} porphyrin has a fully occupied d_{z^2} orbital, which allows only a weak interaction with axial ligands (see Section 1). This also rules out nickel porphyrins for reconstitution. On the other hand, pentacoordinate Zn^{II} porphyrins are known[12]. In fact, the optically excited triplet state has been detected in $[ZnHb]_4$ and [ZnMb] by ESR spectroscopy, and differences have been noted between the porphyrin-globin interaction here and that in hemoglobin and myoglobin[90].

Even a lanthanoid porphyrin, Yb(meso-DME)(acac), with the composition *(3j)*, has recently been reconstituted with apomyoglobin. Being a shift reagent, the paramagnetic ytterbium ion should facilitate the analysis of the NMR spectra of globin[91]. However, since *(3j)* very probably has a different structure from that shown in *(3)* (see Section 7.1), the results cannot be simply applied to myoglobin itself.

7. Variation III: Exotic Metal Porphyrins

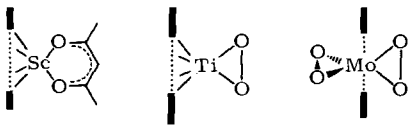
The idea of varying the central metal in hemoglobin can be taken further, but we shall mention here only two types of metal porphyrins, namely the complexes of some d-electron-deficient ("early") transition metals, and the ruthenium and osmium derivatives, with the heavier central atoms from the same group in the periodic table as iron, examples being the carbonylmetal porphyrins *(7c)* and *(7d)*, which are analogous to carbonylheme *(7b)* but much more stable. From a chemical point of view, these are "exotic" metal porphyrins, which cannot be prepared by the usual methods such as reactions (b), and have been reported only recently[3–9]. Though equally interesting, the porphyrin derivatives of technetium and rhenium[7], and of rhodium[92], are less relevant here, because the first two contain two metal ions per porphyrin ligand (like the alkali metal porphyrins[2–6]) and therefore do not belong to any of the coordination types presently under discussion, while the rhodium derivatives are more suitable as models for vitamin B_{12} than for hemoglobin. This incidentally also applies to cobalt porphyrins, which form a great variety of alkyl-metal and aryl-metal derivatives.

The early transition metals give unusual coordination geometries in their oxidation states being sometimes normal, while osmium porphyrins display a larger variety of oxidation states and axial ligands than their iron or ruthenium analogs.

7.1. Unusual Coordination Geometries

Figure 2 shows the coordination types A—C, which are "normal" for the porphyrin system. In principle, besides the *trans* arrangement, a *cis* configuration D is also possible in the presence of two axial ligands L. According to *Schneehage*, the scandium porphyrins[38] can be obtained from tris(2,4-pentanedionato)scandium $Sc(acac)_3$ and the corresponding porphyrin in molten imidazole by reaction (m), an example being Sc(OEP)(acac)[9,93]. On the basis of the IR and NMR spectra, the *cis* configuration N has been chosen for these scandium complexes.

$$Sc(acac)_3 + H_2(OEP) \rightarrow Sc(OEP)(acac) + 2\,H(acac) \qquad (m)$$



N P Q

Initial IR-spectroscopic work[9, 93, 94], followed by X-ray structure analysis (Fig. 6)[95], has demonstrated on bis(acetato)-zirconium(IV)porphyrin and bis(acetato)hafnium(IV)porphyrin of formula M(OEP)(OAc)$_2$ (M = Zr, Hf) that porphyrin complexes with a metal ion can also have a coordination number higher than 6 (in this case 8). This high coordination number had already been established by *Lux* and *Hoppe*[96] for sandwich-type phthalocyanine derivatives such as U(Pc)$_2$, and it is also typical of hafnium and thorium porphyrins such as Hf(OEP)(acac)$_2$[97] and Th(TPP)(acac)$_2$[98]. Prompted by this work, other authors demonstrated the coordination number 7, again with *cis*-axial ligands, in the case of two niobium(V) porphyrins, namely the complexes Nb(TPP)O(OAc)[99] and $Nb_2O_3(TPP)_2$[94, 99, 100]. It seems that this unusual geometry can exist only in the presence of a transition metal ion of the acceptor class A ("hard acid", early transition metal) and a bidentate chelate ligand L⌒L, for which acetate and 1,3-diphenyl-1,3-propanedionate have been used besides 2,4-pentanedionate.

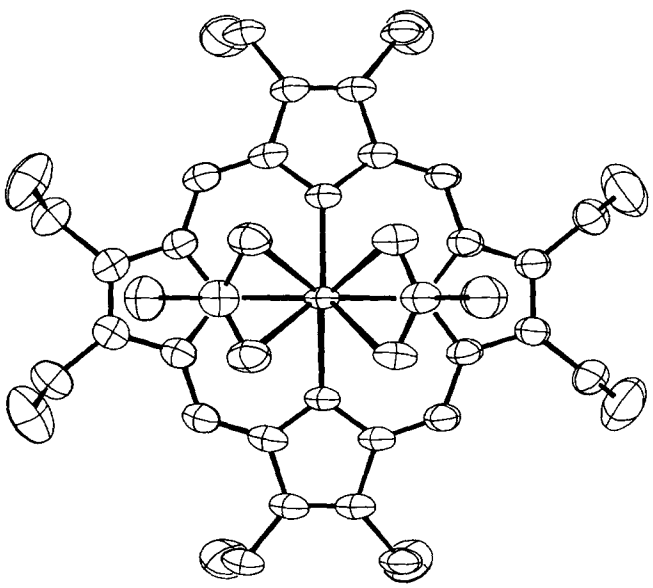


Fig. 6. Results of crystal structure analysis of an octacoordinate hafnium(IV) porphyrin Hf(OEP)(OAc)$_2$ [95]. Two of the pyrrole nitrogens are hidden under the two carboxyl carbons of the acetate groups; the four nitrogens of the porphyrin ligands and the four oxygens of the acetate ions form a distorted square antiprism. The Hf^{IV} ion lies 100 pm above the porphyrin plane.

If the "bite" is reduced, *i.e.* if the distance between the L atoms in the chelate Ligand L⌒L is decreased, then not only relatively large ions like Sc^{III}, Zr^{IV}, and Nb^{V} but also smaller ones like Ti^{IV} and Mo^{VI} can enlarge their coordination sphere in the porphyrin system. According to *Fournari*[101] and *Weiss*[102], peroxide groups with a bidentate linkage can smoothly replace double-bonded oxygen in these complexes—as also in many oxo complexes—by the action of hydrogen peroxide, *e.g.* in reaction (n).

$$\underset{(7e)}{TiO(OEP)} + H_2O_2 \rightarrow \underset{P}{TiO_2(OEP)} + H_2O \qquad (n)$$

X-Ray crystallographic investigations have shown that the peroxotitanium(IV) porphyrin TiO_2(OEP) has configuration P[101], which corresponds to D or N. Particularly remarkable is the bis(peroxo)molybdenum(VI) compound Mo(O$_2$)$_2$(TPP) with configuration Q, which has also been proved by X-ray crystallography.

The complex is obtained from oxomolybdenum(V) porphyrins[9, 93, 103, 104] described before, by oxidation and ligand exchange as in reaction (n)[102]. This complex is the *trans* analog of octacoordinate zirconium porphyrins (Fig. 6). The two peroxide ligands are staggered (S_4 symmetry) when the molecule is viewed normally to the porphyrin surface and are ecliptic to the N atoms of the porphyrin system.

P and Q are the first examples of porphyrin complexes that exhibit structural elements of the Griffith configuration G of the dioxygenyliron system. The complexes can be formally regarded as mono- or bis(dioxygen) adducts of Ti(OEP) or Mo(TTP), but these derivatives of Ti^{II} and Mo^{II} are as yet unknown, and O_2 cannot be detached from P and Q. It is strange though that P and Q have come to light just now as more and more arguments are being found against the presence of G in [Hb·O$_2$].

According to the IR spectra, the lanthanoid porphyrins such as Yb(meso-DME)(acac) mentioned in Section 6.2 also possess bidentate pentanedionate ligands and therefore exist in a *cis* configuration D, like the scandium porphyrins whose discovery prompted the synthesis of the lanthanoid derivatives[91]. This is understandable in view of their large ionic radii; even heptacoordinated species like Yb(meso-DME)(acac)H$_2$O must be considered. However, a *cis* configuration of the axial ligands lead to the formation of a metalloglobin with a rather unnatural conformation in reconstitution experiments with apoglobins, even if the proximal histidine adds on to the lanthanoid ion at all.

7.2. An Increased Variety of Axial Ligands in the Case of Osmium Porphyrins

Up to 1971 all the known methods of metal insertion failed to introduce osmium into the porphyrin system. Finally *Rohbock* succeeded in synthesizing the carbonylosmium(II) porphyrin Os(OEP)CO(Py) *(7d)*[105] by the dropwise addition

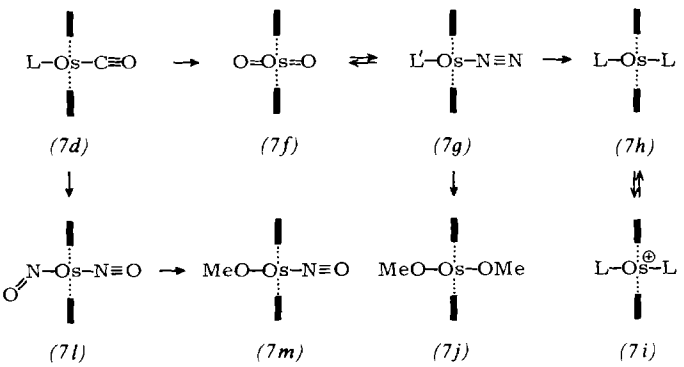


Fig. 7. Schematic representation of the essential chemistry of osmium porphyrins [Os(OEP) *(7)*; for *(7d)*, *(7f)*—*(7j)* also with Os(TTP) *(6j)*].

of a cold solution of osmium tetroxide in diethylene glycol monomethyl ether to a solution of octaethylporphyrin in the same solvent, kept at about 200 °C. The CO ligand was formed by oxidation and decarbonylation of the primary hydroxy groups of the solvent; pyridine was added at the crystallization stage. Figure 7 shows the essential chemistry of osmium porphyrins, based on *(7d)*. The fundamental differences from the chemistry of iron porphyrins (Fig. 5) are as follows:

1) Osmium can have more oxidation states (+2, +3, +4, and +6) than iron (+2 and +3) in compounds stable in air.

$$\underset{(7d)}{Os(OEP)CO\cdot Py} \xrightarrow[CH_2Cl_2/MeOH]{CH_3CO_3H/H_2O} \underset{(7f)}{OsO_2(OEP)} \qquad (o)$$

trans-Dioxoosmium(VI) porphyrin *(7f)*[106], which can be prepared from *(7d)* with peracetic acid in dichloromethane/methanol/H_2O as shown in reaction (o), was the first example of the highest oxidation state of a metal that can be achieved in a porphyrin; *(7f)* is an important starting material for further reactions (Fig. 7).

2) The adducts of Os^{II} porphyrins formed with small π-acceptor molecules are much more stable than those of the Fe^{II} analogs. This can be explained by the stronger π-donor character of the Os^{II} ion and the consequently reinforced metal-ligand back-donation, because its occupied 5d orbitals extend further out and penetrate through the π^* molecular orbitals of the ligands better than do those of the Fe^{II} ion. As a result, the carbonylosmiumporphyrin *(7d)*, for example, is so stable that it can be vaporized at about 200 °C in the high vacuum of a mass spectrometer, and the molecular ion can be detected[105]. The replacement of Fe^{II} by Os^{II} in hemoglobin is therefore pointless, because the "osmoglobin" would absorb even traces of carbon monoxide, and would gradually become irreversibly poisoned.

3. Owing to the stronger "penetration" of the d orbitals into the π^* level of the porphyrin ligand on the one hand and of the axial ligands on the other, the spectroscopic effects (*cis* and *trans* effects[39b, 57]) accompanying the changes in the axial ligands are much more pronounced with Os^{II} porphyrins than with Fe^{II} porphyrins, where they are just outside the accuracy of the measurements. In this connection, Os^{II} porphyrins permit a much more accurate study of the electronic interactions[107], the results of which can be applied to Fe^{II} porphyrins.

The strong d_π donor action of the Os^{II} ion *e.g.* in Os(OEP)CO(THF)[105] is also manifested in the very low frequency of the CO stretching vibrations, namely $\nu_{CO} \approx 1900\,cm^{-1}$. According to *Chatt*'s rule, in the case of such low values one can expect the existence of dinitrogen derivatives that are isosteric with the CO complexes and in which the N_2 molecule is accordingly bonded end-on[108]. *Smith* indeed obtained the first isolable dinitrogen complex of a metal porphyrin by reducing the dioxoosmium(VI) complex *(7f)* with hydrazine hydrate in THF as shown in reaction (p). The resulting Os(OEP)N_2(THF) *(7g)* can be kept in the solid state in air for a few days, but undergoes rapid autoxidation in solution, re-forming the Os^{VI} porphyrin *(7f)*; in methanol,

$$\underset{(7f)}{Os(OEP)O_2} + N_2H_4 + THF \rightarrow \underset{(7g)}{Os(OEP)N_2(THF)} + 2H_2O \qquad (p)$$

the autoxidation stops at the tetravalent osmium stage, with the formation of the bismethoxide $Os(OEP)(OMe)_2$ *(7j)*[109]. This again shows the labilizing effect of the porphyrin system on the axial ligands, discussed in Section 5. The dinitrogenpentaamminoosmium(II) cation $[Os(NH_3)_5N_2]^{2+}$, which has been known for a long time, is much more stable not only in the salt-like solid state but also in solution[110]. Accordingly, the displacement of the coordinated N_2 molecule, so far the only reaction of *(7g)*, could be used for preparative purposes as shown in reaction (q)[109, 111].

$$\underset{(7g)}{Os(OEP)N_2(THF)} + 2L \rightarrow Os(OEP)L_2 + N_2 + THF \qquad (q)$$

L = 1-MeIm, Py, MeCN, PR_3

This gave "osmochromes" such as $Os(OEP)Py_2$ *(7h)*, which are analogous with the hemochromes *(5a)* and are otherwise difficult to obtain. Like the hemochromes, these can be oxidized electrochemically into cationic complexes—"osmichrome salts", such as $[Os(OEP)Py_2]PF_6$ *(7i)*[111]. In comparison with the hemochrome/hemichrome system, however, the osmochrome/osmichrome system is much more resistant to substitution of the axial ligands and can therefore be characterized better. As in the case of iron porphyrins, this gives an opportunity to increase our knowledge of the mode of action of cytochromes[57].

Two further dinitrogen complexes, Os(OEP)N_2(DMF) *(7k)*[111] and Os(TTP)N_2(THF) *(6k)*[112], have recently been isolated. The order of the frequencies of the NN stretching vibrations [$\nu_{NN} = 2035\,cm^{-1}$ *(7k)* < $2042\,cm^{-1}$ *(7g)* < $2050\,cm^{-1}$ *(6k)*] shows that, as a donor ligand in the *trans* position, dimethylformamide increases the Os—N back-donation, probably because of its π-donor action, which is more pronounced than that of THF[57, 77] (*trans* effect), while the tetra(*p*-tolyl)porphyrin ligand in *(6k)* decreases the Os—N back-donation (*cis* effect) owing to its π-acceptor capacity, which is greater than that of the octaethylporphyrin system.

A strong *trans* effect has also been found in the case of the nitrosyl complexes *(7l)* and *(7m)*[107]. While the dinitrosyl complex $Os(OEP)(NO)_2$ *(7l)*, which can be prepared from the carbonyl derivative *(7d)* in an aprotic medium, decomposes with evolution of NO when heated to above 100 °C, the nitrosylmethoxo derivative Os(OEP)NO(OMe) *(7m)*, which is obtained by reacting *(7l)* with methanol, can be vaporized without decomposition in the high vacuum of a mass spectrometer, giving a molecule-ion. The dinitrosyl complex *(7l)* can be chromatographed and crystallized at room temperature, unlike its iron analog *(5j)* (Fig. 5), which has been detected only at −196 °C; this shows again how much the replacement of Fe^{II} by Os^{II} stabilizes adducts formed between small molecules and the metal porphyrin system. The diamagnetism and the IR spectrum of *(7l)* point to a rare *trans* arrangement of both NO species, caused by the porphyrin system.

Another *cis* effect exerted on the visible spectrum embodies the "rule of bathochromism" (see below), which serves to identify the adducts of small molecules to metal porphyrins and can be worked out particularly well in the case of the osmium porphyrins, because of the particularly pronounced effects in their case[57]. On going from hemochromes to car-

bonylhemochromes [sequence *(5a)* → *(5b)* → *(5g)*, Fig. 5], there is a 10—14 nm bathochromic shift in the absorption maximum with the longest wavelength ("α band", Fig. 3). In contrast, the corresponding shift is by 30—33 nm in the carbonylosmium porphyrins *(7d)* and osmochromes *(7h)*[57]. The greater is the π-acceptor capacity of the axial ligand, the greater is this shift. Accordingly, there is a bathochromic shift of the α-band in the series Os(OEP)Py_2 *(7h)*, 510 nm < Os(OEP)N_2(THF) *(7g)*, 523 nm < Os(OEP)CO(Py) *(7d)*, 540 nm < Os(OEP)NO(OMe) *(7m)*, 567 nm, corresponding to the series Py < N_2 < CO < NO^+ along which the π-acceptor strength increases[107]. If this rule is applied to the α bands of hemoglobins [Hb] (555 nm), [Hb·CO] (569 nm), [Hb·O_2] (577 nm, Fig. 3), and [Hb·NO] (575 nm), we find that the electron delocalization to the π-acceptor ligands is found to be about the same for NO and O_2 and in either case greater than with CO. This rule also holds for cobalt(II)-porphyrins[77]. *Gouterman* has provided the theoretical basis of this rule by molecular-orbital calculations by the iterative extended Hückel method[113].

The replacement of iron by osmium in hemoglobin to prepare an "osmoglobin" seems highly problematic and troublesome, because the very drastic reaction conditions used for the incorporation of osmium cannot be applied with the labile protoporphyrin system, and besides they lead to the extremely stable CO complex. However, in principle it is now possible to prepare an "osmoglobin". The possibility cannot be altogether excluded that it might function as an N_2 carrier.

7.3. Ruthenium Porphyrins and Their Comparison with Iron and Osmium Porphyrins

Ruthenium porphyrins were first synthesized by *Fleischer*[114] in 1969 and were then further investigated mainly by *Tsutsui*[7, 55a, 55b], *Holm*[55c], and *Whitten*[115, 116]. However, their axial-ligand chemistry is underdeveloped in comparison with iron and osmium porphyrins[6]. Only the carbonyl complexes *e.g.* Ru(TPP)CO(Py) *(6l)*[117], the ruthenochromes, *e.g.* Ru(OEP)Py_2 *(7n)*[113, 118], and the nitrosylmethoxide complex Ru(OEP)NO(OMe) *(7p)*, which also obey the "rule of bathochromism"[113], have been properly characterized. The bathochromic shifts of the α bands in the series Ru(OEP)Py_2 *(7n)*, 521 nm < Ru(OEP)CO(Py) *(7c)*, 549 nm < Ru(OEP)NO(OMe) *(7p)*, 572 nm lie between the corresponding values for the compounds of the Fe^{II} and Os^{II} series. The CO frequencies decrease from Fe(OEP)CO(Py) *(7b)*, 1967 cm^{-1} through Ru(OEP)CO(Py) *(7c)*, 1925 cm^{-1} to Os(OEP)CO(Py) *(7d)*, 1902 cm^{-1}. Both results show that the back-donation ability of the central metal ion and thus also the bond strength for small π-acceptor molecules increase along the series: Fe^{II} < Ru^{II} < Os^{II}.

As regards their redox behavior, however, ruthenium porphyrins occupy a surprising position: the half-wave potentials of the metal(II/III) state, determined by cyclic voltammetry with respect to a calomel electrode, rise in the series Os^{II} < Fe^{II} < Ru^{II}, *i.e.* Os(OEP)Py_2 *(7h)* −0.37 V[111], Fe(OEP)Py_2 *(7q)* −0.15 V[57, 119], Ru(OEP)Py_2 *(7n)* −0.02 V[57, 115, 119]. This effect, which is also exhibited by the carbonyl derivatives, agrees with theoretical results based on molecular-orbital calculations[113].

The relatively high Ru^{II}/Ru^{III} redox potentials mean that Ru^{II} porphyrins have a correspondingly weaker driving force for autoxidation, and they should therefore be interesting candidates for reversible oxygenation (see the closing remarks in Section 4). Indeed, recent results indicate that a labile bis(acetonitrile)ruthenochrome, Ru(OEP)$(MeCN)_2$ *(7r)*, is capable of undergoing reversible oxygenation even at room temperature[120]! However, the dioxygen adduct of *(7r)*, postulated only on the basis of spectrophotometric and presumably also gas-volumetric findings, does not obey the "rule of bathochromism": its α band shows an appreciable hypsochromic shift with respect to that of the carbonyl complex. This does not mean that this adduct does not exist, but it conflicts with a monodentate bent bonding state of its RuO_2 unit according to Pauling's model E. It is possible that we are faced here with a peroxoruthenium(IV) system of configuration G, which according to the results given in Section 7.1 for metal porphyrins can no longer be disregarded and which, according to *Vaska*[71] is to be expected anyway for ruthenium, together with the ability of liberating O_2 again at room temperature. The product of autoxidation of *(7r)*, which is slower than oxygenation, has not yet been identified. Owing to the more highly negative redox potential[57] the kinetically more stable Os^{II} analog Os(OEP)$(MeCN)_2$ *(7s)* merely undergoes irreversible autoxidation to OsO_2(OEP) *(7f)*[111].

The existence of nitrogen-carrying ruthenium porphyrins[116, 120], postulated on the basis of spectrophotometric findings only, should be viewed with skepticism since such compounds also do not obey the "rule of bathochromism" and purportedly exist as *trans* ligands in the presence of pyridine or other N-donors. (The latter also applies in the case of the previously discussed, but still unknown Fe(proto-DME)N_2(Py)[121].) Since even dinitrogenosmium(II) porphyrins are cleaved by any other N-donor[109, 112, 113], such behavior would be all the more likely in the case of the more labile Fe^{II} and Ru^{II} analogs which must therefore be regarded—on the basis of experimental evidence thus far—as doubtful species.

On the whole, what has been said about an osmoglobin (Section 7.2) applies also to ruthenoglobin.

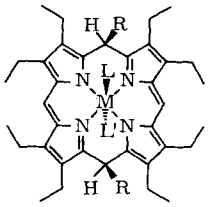
8. Variation IV: Iron Porphodimethenes

The final variation to be presented is the porphodimethene system, a further, not only sterically but also electronically modified porphinoid ligand system akin to an α,γ-dihydroporphyrin. The synthesis of the configuratively important carbonyl(α,γ-dimethyloctaethylporphodimethenato)pyridineosmium(II) *(16a)*[122] might serve as example for the synthesis of such complexes (see Table 5) by *Puppe*'s reductive methylation of porphin complexes[123] according to reaction (r).

$$\underset{(7d)}{\text{Os(OEP)CO(Py)}} \xrightarrow[2.\ 2\,\text{MeI}]{1.\ 2e^{\ominus}} \underset{(16a)}{\text{Os(OEPMe}_2\text{)CO(Py)}} \qquad \text{(r)}$$

On the basis of crystal structure analysis by *Scheidt*, the molecule *(16a)* carries the two newly introduced methyl groups in a *syn*-axial position to the carbonyl group, like a chimney on the tetrapyrrole system, which is folded like a roof, with

the pyridine molecule suspended under the ridge of the roof (Fig. 8). Like the further structure analyses of nickel(II)- and titanylporphodimethenes[124], this picture immediately prompts one to try—as is being done now by *Lay*—to introduce bulky substituents somehow at the iron center in place of the methyl groups, in order to obtain myoglobin models of the type described in Section 6.



(16)

Table 5. Examples of porphodimethenes $M(OEPR_2)LL'$ *(16)*.

	M	R	L	L'
(16a)	Os	Me	CO	Py
(16b)	Fe	Me	Py	Py
(16c)	Fe	t-C_4H_9	OH	
(16d)	Fe	Me	O/2 [a]	

[a] μ-Oxo complex of type *(5e)*.

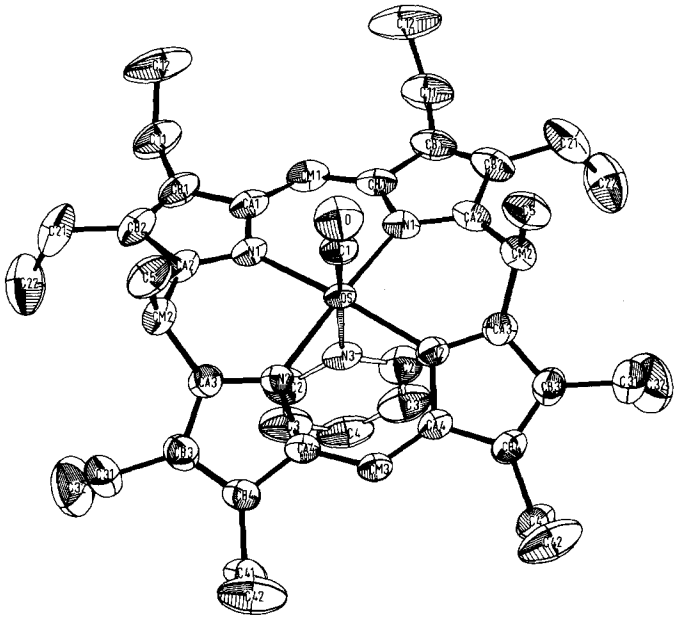


Fig. 8. Results of crystal structure analysis of a metal porphodimethene complex $Os(OEPMe_2)CO(Py)$ *(16a)* [d(Os—C) = 183, d(C—O) = 115, d(Os—N_{Py}) = 223, d(Os—$N_{(P)}$) = 207 pm].

However, it is very difficult to investigate the iron porphodimethenes, for two reasons:

1) Reductive ring alkylation does not work with Fe^{II} porphyrins, so that the iron porphodimethenes must be synthesized in a different, complicated way, which is of no interest to us here[125].

2) The double interruption of the porphyrin chromophore leads to much less informative visible spectra, which sometimes exhibit only a broad band at about 460 nm (this band is reponsible for the orange color of the porphodimethenes). For this reason, the complexing reactions corresponding to those shown in Figure 5 cannot be monitored spectrophotometrically as in the case of Figure 3.

3) The decreased aromaticity lowers the π-acceptor capacity of the porphinoid ligands and may thus make the oxygen uptake irreversible[126] by lowering the redox potential at the porphodimethene-hemochrome [*(16b)*, −0.30 V with respect to a calomel electrode[119]].

However, with the isolation of the di-*tert*-butylporphodimethene complex *(16c)*, the first mononuclear hydroxoiron(III) complex with a porphinoid ligand system has been prepared in substance. The constitution of this complex has been ascertained by chemical analysis, IR spectrum ($\nu_{OH} = 3661\ cm^{-1}$), magnetic measurements ($\mu_{eff} = 5.7$ B.M.), ESR spectrum ($g_\perp = 5.83$), and the Mössbauer spectrum[127]. In the porphodimethene complex *(16c)* condensation with the iron hydroxide group into a binuclear complex occurring in the step *(5f)* → *(5e)* (Fig. 5) is inhibited on both sides: at the top by the bulky *tert*-butyl groups, and at the bottom by the roof-like folding of the ligand surface, which does not even allow the formation of a greatly over-extended Fe—O—Fe bridge.

On the other hand, *(16d)*, a μ-oxo complex of α,γ-dimethylporphodimethene corresponding to type *(5e)*, is easy to prepare[125]. IR spectra and magnetic measurements[51b] indicate that axial methyl groups impair its Fe—O—Fe bridge, but this is not sufficient to prevent condensation.

Owing to its similarity to [Mb·OH] [cf. *(4e)*], the hydroxide *(16c)* can be regarded as a "partial metmyoglobin model", partial because there is no proximal histidine *trans* to the OH group. An accurate analysis of the physical properties of *(16c)* might be useful in the continuing investigation of the physics of metmyoglobin[19e].

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Chemical Ionization—A Mass-Spectrometric Analytical Procedure of Rapidly Increasing Importance

By Wilhelm J. Richter and Helmut Schwarz[*]

The mode of ionization of a molecule has a strong influence on its behavior in the mass spectrometer and thus on the information that can be obtained from its mass spectrum. In chemical ionization a reagent gas, *e.g.* methane, is first ionized by electron impact. The ions formed in ion-molecule reactions, in particular $[CH_5]^+$, $[C_2H_5]^+$, and $[C_3H_5]^+$, then react "chemically" with the substrate M in fast acid/base type reactions to form ions of the type $[MH]^+$, $[M(C_2H_5)]^+$, *etc.*, which subsequently fragment to various extents. Alternatively, chemical ionization can be effected by charge exchange, in that ions of a reagent gas, *e.g.* $[He]^{+\bullet}$, react with the substrate M to form molecular ions $[M]^{+\bullet}$. Chemical ionization can thus be conducted in a more or less mild fashion and the extent of the fragmentation can be controlled over a very wide range.

1. Introduction

Given the use of a suitable instrument, the versatility of mass spectrometry[**] permits the investigation of a wide variety of problems ranging from investigations of primarily scientific character to investigations of practical and highly topical significance. Studies of the kinetic, thermodynamic, and chemical behavior of ions in the gas phase, including studies of extremely fast to relatively slow reactions on the picosecond to millisecond time scale, exploration of surface properties of solids, structure elucidation of unknown substances, as well as detection and quantitative determination of known substances are but a few examples to which mass spectrometry can be successfully applied[1]. Mass spectrometry qualifies especially for analytical applications because of its very high sensitivity (present detection limits about 10^{-14} g) and because of the wealth of information afforded, quite unattainable by any other routine method of instrumental analysis for minute sample size. As judged by the number of published papers and instruments in use, analytic chemistry represents the principal field of application of the method. Mass spectrometry is almost indispensable for trace analysis, especially in the environmental, biological, and medical sciences. In depth, its potential and scope are demonstrated by geochemical, paleontological, archeological, and cosmochemical studies—*e.g.* in the Apollo and Viking projects.

In analytical applications the reliable determination of molecular weights (when using high-resolution instruments also the determination of molecular formulas), along with correlation of fragmentation with structural features are often the main objectives. In conventional ionization by electron impact, limitations or difficulties may arise because the sample has to be ionized in the gas phase, yielding molecular ions $[M]^+$ often insufficiently stable to permit detection. Further limitations may arise because insufficiently volatile or thermally labile compounds can pyrolyze or isomerize before ionization takes place and because isomerization can also occur after ionization.

In recent years it has become possible to overcome these disadvantages to a considerable degree by an extension of the methodology. So far as the correlation of fragments with structural features is concerned, collisional activation (CA) mass spectrometry[2] and other techniques[3] now make it possible to verify structures of ions. Thus conclusions can be drawn from fragments on a much better-founded basis regarding the structure of molecular ions and, hence, also about the structure of intact molecules. In the determination of molecular weights of intact substrates there have even been several breakthroughs, represented by three new techniques: 1) Field desorption mass spectrometry (FD), developed by *Beckey* and his associates[4a], especially in its variant of cationization[4b-4d]; 2) the still very recent development of ionization by radioisotopes (californium-252 source)[5]; and 3) the method of chemical ionization (CI)[*] developed by *Munson* and *Field*[6], which constitutes the subject of the present article. The first two of these procedures allow very mild ionization of the substrate, *i.e.* ionization with little excess energy transfer; owing to the suppression of fragmentation, well-defined molecular ions are produced, or their adducts with protons or alkali-metal ions. The two processes truly extend the area of application of mass spectrometry in that, unlike electron-impact ionization (EI), they permit the study of intact compounds that do not volatilize without decomposition. Chemical ionization (CI) shares only the advantage of mild ionization; yet, in contrast to the FD techniques, the amount of fragmentation can be controlled within a wide range, whereby the proportions of information about molecular weight on the one hand and structure on the other can be adapted,

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[**] Abbreviations: amu, atomic mass units; CD, charge exchange; CI, chemical ionization; EI, electron-impact ionization; FD, field desorption; FI, field ionization; GC, gas chromatography; ICR, ion cyclotron resonance; MS, mass spectrometry; PA, proton affinity; RE, recombination energy; SIM, selected ion monitoring; TIC, total ion current.

[*] The term "chemical ionization" (CI) is not synonymous with chemi-ionization. Chemi-ionization achieves ionization of a substrate by interaction with electronically excited neutral particles [8].

almost at will, to requirements by varying the experimental conditions. Chemical ionization is therefore often an alternative to electron-impact ionization, whereas the two other modes of ionization represent more or less complementary techniques.

In accordance with its special merits and promise[*] for modern mass-spectrometric analysis, chemical ionization has been discussed in several earlier reviews[1b, 7] sometimes placing emphasis on special aspects of the topic; in the present article we can thus concentrate on some of the more recent viewpoints and results after first describing the principles of the phenomenon.

2. Physicochemical Aspects

2.1. Production of the Ionizing Plasma and Ionization of the Substrate

When electron-impact ionization of a compound, *e.g.* methane, is carried out at *ca.* 1×10^{-3} bar in contrast to the usual high-vacuum conditions (*ca.* 10^{-9} bar), the molecular ions and fragments produced [eq. (a)] can react further in rapid ion/molecule reactions[9] with neutral methane molecules as a result of the diminished mean free path. Concentrations of "secondary" and "tertiary" ions are thus built up [eq. (b)—(h)], in dependence on the pressure, temperature, and instrumental parameters that determine the residence time of the charged particles in the collision chamber (ion source). At this operating pressure of about 1×10^{-3} bar 95% of the total ion current is carried by the following species: $[CH_5]^+$ (48%), $[C_2H_5]^+$ (41%), and $[C_3H_5]^+$ (6%).

$$CH_4 + e^- \rightarrow [CH_4]^{+\bullet}, [CH_3]^+, [CH_2]^{+\bullet}, [CH]^+, [C]^{+\bullet}, [H_2]^{+\bullet}, [H^+] \quad (a)$$
$$[CH_4]^{+\bullet} + CH_4 \rightarrow [CH_5]^+ + CH_3^\bullet \quad (b)$$
$$[CH_3]^+ + CH_4 \rightarrow [C_2H_5]^+ + H_2 \quad (c)$$
$$[CH_2]^{+\bullet} + CH_4 \rightarrow [C_2H_4]^{+\bullet} + H_2 \quad (d)$$
$$[CH_2]^{+\bullet} + CH_4 \rightarrow [C_2H_3]^+ + H_2 + H^\bullet \quad (e)$$
$$[CH]^+ + CH_4 \rightarrow [C_2H_2]^{+\bullet} + H_2 + H^\bullet \quad (f)$$
$$[C_2H_5]^+ + CH_4 \rightarrow [C_3H_7]^+ + H_2 \quad (g)$$
$$[C_2H_3]^+ + CH_4 \rightarrow [C_3H_5]^+ + H_2 \quad (h)$$

If such a "methane plasma" contains as an additive a second compound M in a concentration smaller by orders of magnitude (generally 1: $<10^{-4}$), it will be converted into ions not directly by primary electron impact (a physical process), but by ion/molecule reactions with the above species (*i.e.* by chemical processes). Not only can the $[CH_5]^+$[**] and the $[C_2H_5]^+$ ions function as Brønsted acids with respect to M in proton-transfer reactions [eqs. (i) and (j)], but also the $[C_2H_5]^+$ ion can function as a Lewis acid [eq. (k)] in the formation of collision-stabilized complexes. In the formation of the ions $[MH]^+$ and $[M(C_2H_5)]^+$ ("quasimolecular ions" $[QM]^+$)[***], methane at a pressure of *ca.* 1 mbar (the usual CI working pressure) thus acts as a "reagent gas", the compound M as a CI substrate.

$$[CH_5]^+ + M \rightarrow [MH]^+ + CH_4 \quad (i)$$
$$[C_2H_5]^+ + M \rightarrow [MH]^+ + C_2H_4 \quad (j)$$
$$[C_2H_5]^+ + M \rightarrow [M(C_2H_5)]^+ \quad (k)$$

Besides this acid/base type of substrate ionization, which is often used in practice and which invariably involves "closed shell" ions, in chemical ionization in the widest sense[*], another type of ion/molecule reactions is of importance, in which the substrate is ionized by charge exchange (CE). Such CE processes correspond to the redox-reaction type and, like electron-impact ionization, lead to "true" molecular ions, *i.e.* to species with "open shell" character [eq. (l)]; they occur particularly with reagent gases that contain no H atoms (noble gases, N_2, NO, O_2, CO).

$$[He]^{+\bullet} + M \rightarrow [M]^{+\bullet} + He \quad (l)$$

Like electron-impact ionization, acid/base and also redox-type ionization find a counterpart in the formation of negative ions. Whereas "negative CE" (NCE) occurs by resonance capture of thermal electrons, such as are present in a nitrogen plasma (electron attachment), in "negative CI" of the acid/base type (NCI), proton transfer occurs in analogy to the positive mode (but in the opposite direction) together with formation of addition complexes. Reagent anions such as $[CH_3O]^-$ (*e.g.* from CH_3ONO as the reagent gas [(eq. (m)][11a]) or $[Cl]^-$ (from the substrate itself by dissociative electron addition [eq. (n) and (o)][11b, 11c]) now function as Brønsted or Lewis *bases*, respectively.

$$[CH_3O]^- + R{-}H \rightarrow [R]^- + CH_3OH \quad (m)$$
$$e^- + R{-}Cl \rightarrow [Cl]^- + R^\bullet \quad (n)$$
$$[Cl]^- + R{-}Cl \rightarrow [RCl_2]^- \quad (o)$$

2.2. Energetics of Ionization and Fragment Formation

2.2.1. Thermodynamic Factors

The contributions of processes (i)—(k) to the total ionization of a substrate are in the first place determined by the structure of the substrate and the nature of the reagent gas selected. In general, only exothermic ion/molecule reactions proceed at high rates[9]. In the acid/base case this fundamental condition for chemical ionization is always fulfilled for proton transfer [eqs. (i) and (j)] if the proton affinity (PA)[**] of M exceeds that of the conjugate base (*e.g.* CH_4 or C_2H_4) of the relevant reagent ion ($[CH_5]^+$ or $[C_2H_5]^+$). The PA values of some common reagent gases are listed in Table 1.

[*] The growing importance of chemical ionization can be recognized, by the fact that as few as about 30 papers appeared on this topic in the period from 1966 to 1971 [7i] but more than a thousand up to 1976. We are grateful to Dr. *H.-M. Schiebel*, Technical University of Braunschweig, for his assistance with the literature search.

[**] For the structure of the ion $[CH_5]^+$ and some homologous carbonium ions see [10].

[***] Although this description is, strictly speaking, incorrect [1b, 74], it is retained here for convenience.

[*] Some authors restrict the term "chemical ionization" to this acid/base type of reaction [eq. (i)—(k)] and regard charge-exchange processes [eq. (l)] as a separate type of ionization. Common to both types of ionization is the occurrence of ion/molecule reactions.

[**] Proton affinity (PA) is defined as the standard enthalpy ΔH^0 of the reaction $[MH]^+ \rightarrow M + [H]^+$. For a comprehensive collection of PA values and critical comments on the methods of measurement see [7h] and [12b—12d].

Table 1. Protonating reagent gases, principal reagent ions, and proton affinity (PA) of corresponding conjugate bases (chemical ionization (CI)) [7, 12b, 12d].

Reagent gas	Brønsted acid	PA (kcal/mol)
H_2	H_3^+	101
CH_4	CH_5^+	126
H_2O	H_3O^+	169
CH_3OH	$CH_3OH_2^+$	182
i-C_4H_{10}	t-$C_4H_9^+$	193 (i-C_4H_8)
NH_3	NH_4^+	201

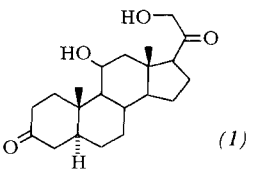
A first consequence of this energy requirement is that some degree of selectivity as to effective ionization of the substrate can be achieved by the choice of the reagent gas. Thus, chemical ionization with NH_3 as the reagent gas $[CI(NH_3)]$, unlike universally protonating chemical ionization with CH_4 $[CI(CH_4)]$, causes no protonation to $[MH]^+$ ions neither in saturated nor non-conjugated unsaturated ketones (PA values $< 200\,kcal \cdot mol^{-1}$[7h, 12]); yet it causes formation of their precursors, *i.e.* of collision-stabilized complexes $[M(NH_4)]^+$, in which (endothermic) H^+-transfer is not completed. However, owing to the increase in proton affinity as a result of conjugation α,β-unsaturated ketones afford high yields of $[MH]^+$ ions under these conditions[13]. A second, no less important consequence of the energetics of the ionization process is that the exothermicity (difference between the PA values of the substrate and of the conjugate base of the reagent ion) controls to a considerable degree the stability of the $[MH]^+$ ions and thus the extent of decomposition into ions of smaller mass with loss of neutral particles (CI fragmentation). In this way, energy-rich reagent ions such as $[H_3]^+$ or $[CH_5]^+$ afford *e.g.* highly excited $[ROH_2]^+$ ions by protonation of alcohols ROH, which, in general, have a much higher proton-affinity than the corresponding reagent-gases (H_2 or CH_4); consequently, these excited ions often decompose completely with loss of water molecules into $[R]^+$ fragments. If, however, $[H_3O]^+$ ions are used for the ionization, (H_2O as reagent gas) relatively stable and thus detectable $[ROH_2]^+$ ions are obtained owing to the smaller PA difference between H_2O and ROH. As mentioned above, this possibility of controlling the fragmentation by appropriate choice of the reagent gas, together with adjustable selectivity, endows the method with a degree of freedom that is of great value in many analytical applications.

A similar situation is encountered in the ionization of substrates by charge exchange (CE). Here too, the reactivity of the initially formed $[M]^{+\bullet}$ ions can be controlled by a suitable choice of the ionizing agent. In this case the energy content of the molecular ions $[M]^{+\bullet}$ is determined[14] by the difference between the recombination energy (RE) of the reagent ions (in eq. (l) of $[He]^{+\bullet}$) and the ionization potential (IP) of M, the latter being in the range 7—12 eV for most organic compounds[14] (RE values for some typical CE reagent gases are listed in Table 2). Correspondingly, when helium is used complete fragmentation often results, while heavier noble gases tend to give molecular ions that fragment to a much smaller extent.

Table 2. Redox type reagent, recombination energy (RE) (ionization by charge exchange (CE)) [12a].

Reagent gas	RE [eV]
He	24.6
Ne	21.5
Ar	15.7
N_2	15.6
Kr	14.0
Xe	12.1

How such energy effects can be used to advantage, and how these two types of chemical ionization can be effectively combined is illustrated in Figure 1. It shows the combined CE/CI spectrum of 4,5α-dihydrocorticosterone *(1)* obtained with a two-component reagent gas system[15] (Ar/H_2O; cf. Section 4.2.1)[15a]. On the one hand, the mild protonation by the weak Brønsted acid $[H_3O]^+$ ($m/e = 19$) leads to $[MH]^+$ ions of remarkable stability for an ROH-type compound (*ca.* 50% relative intensity in spite of the repeated subsequent loss of H_2O) as reliable indicator of molecular weight. On



(1)

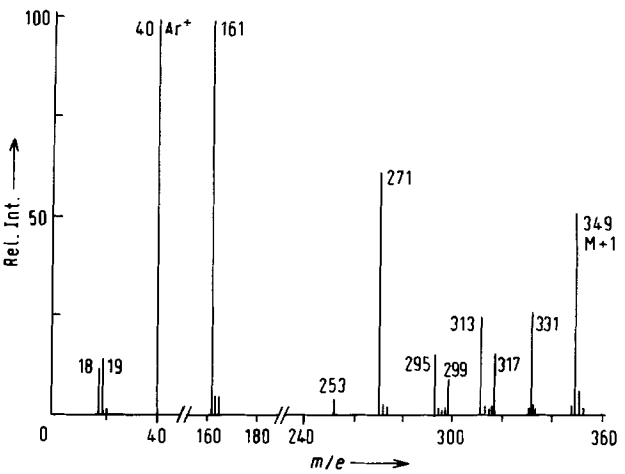


Fig. 1. CE/CI(Ar/H_2O) spectrum of 4,5α-dihydrocorticosterone *(1)*.

the other hand, $[Ar]^{+\bullet}$ ions ($m/e = 40$), act mainly as an aggressive agent of the redox type, simultaneously producing highly unstable $[M]^{+\bullet}$ molecular ions (barely 2% are recorded as such). These latter yield valuable information about the structure because of their marked fragmentation, whose course resembles that observed on electron impact.

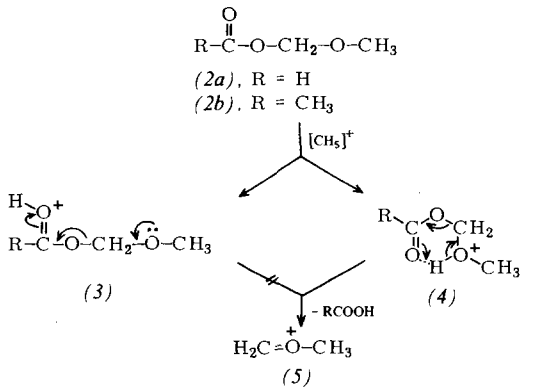
2.2.2. Kinetic Factors

For a given substrate, not only the exothermicity of the ionization process but also the reaction temperature (here in chemical ionization the temperature of the reagent gas) is decisive for the extent of fragmentation, since this temperature provides contributions to the internal energy of the ionized particle. In electron-impact ionization the internal energy of the ions formed in the high vacuum cannot be represented by a Boltzmann distribution, which would be the prerequisite

for an exact mathematical description and formal kinetic treatment of the temperature-dependence of the spectra[*]. In sharp contrast to this, in chemical ionization the large number of collisions of ions with excess reagent gas (the number of collisions lies between 1×10^2 and 2×10^3[7j], depending on pressure, temperature, and residence times of ions in the source) usually permits equilibrium to be sufficiently established in order to assume a Boltzmann distribution of the internal energies of the ions. According to *Field*[7j, 17], the kinetic parameters, *i.e.* activation energy and pre-exponential factor (frequency factor) ν, can consequently be obtained by studies of the temperature-dependence of the fragmentation.

2.3. Special Investigations

The possibility of determining the kinetic parameters of a fragmentation process experimentally is, of course, very valuable for the investigation of fundamental aspects of reaction mechanisms. Thus, it has been shown[18] that the elimination of RCOOH from the $[MH]^+$ ions of methoxymethyl esters *(2)* (Scheme 1) occurs by the same mechanism as their acid-catalyzed solvolysis[19]. From the relatively low values of the frequency factors [$\nu = 4.5 \times 10^9$ and $6.5 \times 10^8\ s^{-1}$ for *(2a)* and *(2b)*, respectively] one can conclude that the rate-determining step is not a simple bond fission [*(3)* → *(5)*] but a rearrangement by way of a relatively highly ordered transition state [*(4)* → *(5)*]. For the methylthiomethyl ester analogous to *(2)* no such strict correspondence of the kinetics of ester fission in the gas and in the condensed phase was observed[20].

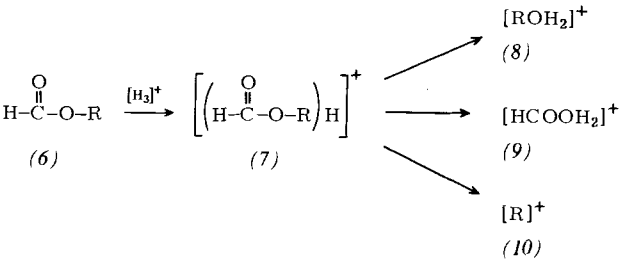


Scheme 1. Fragmentation of methoxymethyl esters *(2)* under CI conditions.

The CI-induced decomposition of benzyl and *tert*-amyl acetate with loss of acetic acid from $[MH]^+$ ions has also been investigated in kinetic detail[17, 21]. $[C_7H_7]^+$ and $[C_5H_{11}]^+$ ions are formed with almost identical activation energies (12.3 and 12.4 kcal × mol^{-1}, respectively), whereas ν for the formation of $[C_7H_7]^+$ is smaller by an order of magnitude than that for the formation of $[C_5H_{11}]^+$. This difference can be accounted for by assuming that, in contrast to *(2)*, the *tert*-pentyl ester decomposes by simple bond fission [analogous to *(3)* → *(5)*], whereas in the transition state of the benzyl ester, rotation around the Ph—CH_2 bond will be restricted as a result of its partial double bond character (stabilization of the incipient carbenium center by π-participation); the reduced number of rotational states of the activated complex is reflected in a somewhat lower frequency factor ν.

The same processes are, however, also of interest because of their temperature effects. When benzyl acetate is protonated with a weak Brønsted acid, *e.g.* $[C_4H_9]^+$ (isobutane as the reagent gas, isobutene as the conjugate base of the reagent ion), then at $T = 37\,°C$ one observes almost exclusively $[MH]^+$ ions. At $T = 196\,°C$, however, the concentration of $[MH]^+$ is considerably reduced and the fragment $[C_7H_7]^+$ now provides the base peak of the spectrum. When $[CH_5]^+$ is used as the protonating agent, only a minimal temperature effect is, however, observed ($[C_7H_7]^+$ is the base peak in the entire temperature range). This contrasting behavior is ascribed to the fact that decomposition of the protonated benzyl ester is a weakly endothermic reaction and can thus occur sufficiently rapidly only on additional *thermal* activation; in protonation by $[CH_5]^+$, a supply of additional thermal energy is unnecessary because of the strong exothermicity of the process (*chemical* activation).

An informative study of the influence of the reagent gas on the nature and the importance of competing fragmentation processes was carried out by *Harrison et al.*[22]. These authors were able to show, again for protonated esters, that—in loose analogy to the quasi-equilibrium theory (QET) governing EI—a process with a relatively high activation energy is kinetically favored if a) the internal energy of the precursor ion considerably exceeds the activation energy and b) the process has a high frequency factor ν (*simple* bond fission). The authors showed that on ionization of *(6)* (Scheme 2) with $[H_3]^+$ (H_2 as the reagent gas) the ion $[R]^+$ *(10)* is formed as the main fragment in an energetically rather demanding but entropically favored process (except when $R = CH_3$). When a weaker Brønsted acid is used the ion *(10)* will be suppressed since condition a) is no longer fulfilled, and the formation of *(8)* and *(9)* will be favored.



Scheme 2. CI fragmentation of alkyl formates *(6)*, R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *i*-C_4H_9, *sec*-C_4H_9.

Finally, it should be mentioned that in chemical ionization structural features of the transition state of S_N2 reactions[23] can be revealed. *Dougherty et al.* and *Brauman* demonstrated which inherent properties[24] (structure of the transition state $[Y \cdots R \cdots X]^-$, nucleophilicity of $[Y]^-$, degree of substitution of R) contribute to the energy and entropy factors of the reaction investigated [eq. (p)]. On comparison of the results with data for the reaction carried out in the condensed phase the authors indirectly established solvent effects.

$$[Y]^- + R{-}X \rightarrow [Y \cdots R \cdots X]^- \rightarrow Y{-}R + [X]^- \qquad (p)$$

[*] The fact that also under EI conditions temperature can considerably influence the extent of fragmentation was emphasized by *Spiteller* [16].

3. The Chemistry of Chemical Ionization

3.1. Classification of Principal Reaction Types[*]

If we neglect the special cases of charge exchange (CE) and "negative" chemical ionization (NCI, NCE), then, owing to the absence of radical reaction centers, most of the behavior of chemically ionized substrates can be ascribed to but a few general modes of reaction such as are familiar from condensed phase ion chemistry. To a first approximation, in which only changes in the relative positions of atoms are considered, we can distinguish the following types of processes: 1) addition reactions, 2) heterolysis, 3) rearrangement, 4) elimination reactions, and 5) replacement (substitution).

3.1.1. Addition Reactions

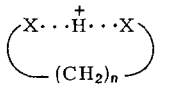
Irrespective of the nature of the newly formed bond, we may consider, for example, the formation of collision-stabilized complexes (described in Section 2.1) of the substrate M with reagent ions (in general with an electrophile $[E]^+$) as an *intermolecular* addition [eq. (k)]. Besides the "classical" electrophiles $[C_2H_5]^+$ and $[C_3H_5]^+$ of the methane plasma, $[i\text{-}C_4H_9]^+$ ions from isobutane, $[NO]^+$[14b,25], $[SiMe_3]^+$[26], and recently $[Li]^+$[27] are of importance. Relatively long-lived adducts are obtained through formation of regular two-electron bonds from substrates with nucleophilic centers (π-electrons of multiple bonds, functional groups X with lone electron pairs). If these centers are basic heteroatoms (*e.g. in* X), this is also true for the adducts $[M(NH_4)]^+$ mentioned above, in which partial bonds are responsible for complex formation (hydrogen bonds $M\cdots H\cdots NH_3$ and perhaps further H-bonds in chelate-like structures when M contains additional basic centers), and for the $[M_2E]^+$ cluster ions[28] that arise under certain conditions (relatively long ion extraction times, high partial pressure of M). Common to all these stable adducts is their analytical significance for reliable molecular weight determination of unknown compounds (cf. Sections 5.1.1 and 5.1.2).

As opposed to these long-lived products of addition reactions, short-lived collision complexes can be recognized only indirectly, due to their rapid decomposition into fragments of often unexpected composition. Formation of complexes of this type with X-substituted arenes by $[CH_5]^+$ and $[H_3]^+$, *i.e.* strong Brønsted acids, was demonstrated only recently[29]. In both cases HX was eliminated from these complexes. In the net result, this corresponds to the unexpected substitution of X by CH_3 or H [eqs. (q) and (r)].

$$[CH_5]^+ + FC_6H_4R \rightarrow [(FC_6H_4R)CH_5]^+ \rightarrow [(CH_3C_6H_4R)H]^+ + HF \quad (q)$$

$$[H_3]^+ + FC_6H_4R \rightarrow [(FC_6H_4R)H_3]^+ \rightarrow [(C_6H_5R)H]^+ + HF \quad (r)$$

Hydrogen bonding, for example, in $[MH]^+$ ions of specific bifunctional compounds can be regarded as an *intramolecular* addition reaction, *i.e.* as counterpart to the formation of bimolecular adducts $[ME]^+$ and $[M_2E]^+$. Corresponding formation of cyclic structures *(11)* from α,ω-diamines[30] and α,ω-dimethoxyalkanes[31] is, *e.g.*, reflected in the proton affinities (which are higher than those of analogous monofunctional compounds) and also by strongly negative protonation entropies. Both *ab initio* calculations[32] and the correlation of thermochemical data with the ring sizes of *(11)* suggest linear geometry of the $(X\cdots H\cdots X)$ bonds.



(11), X = NH_2, OH, OCH_3, OAc, SH; $n > 2$

In conformationally mobile systems macrocyclic structures of the type *(11)* can be formed with up to 49 ring members[33]; as is to be expected, with short-chain diols the entropically favored ring formation does not take place if triple bonds or *trans*-double bonds are present[34]. Consequences of the formation of such internal adducts for fragmentation are discussed in Section 3.1.5.

3.1.2. Heterolysis

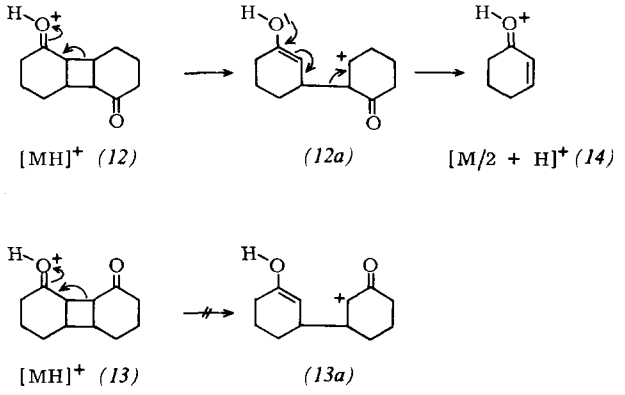
Whereas addition reactions can occur both intermolecularly or intramolecularly, heterolysis must, by definition, be an intramolecular reaction. Effecting the simple cleavage of a bond, heterolysis is the counterpart of an addition reaction. The most simple, though not directly observable case of heterolysis would be the reversal of eq. (k); such a reaction is, in principle, possible on thermodynamic grounds, since dissociation and recombination energies are equal; in practice, the reverse reaction is largely prevented by stabilizing collisions with neutral molecules of the reagent gas. Heterolytic decomposition of $[MH]^+$ ions (M = RX) is, however, very often directly observable; examples in Section 2.3 are the $CI(H_2)$-induced decomposition of the *O*-protonated alkyl formates *(7)* to form the alkyl ions *(10)* (Scheme 2) or of protonated *tert*-amyl acetate in the temperature study discussed. In general, the extent of heterolytic fission of protonated RX compounds [eq. (s)] under standard conditions (same reagent gas, same temperature, same residue R) is, to a first approximation, inversely proportional to the ionization potential of X and to the basicity of HX[7j,35]. The $[R]^+/[RXH]^+$ ratios thus increase within a series of compounds RX in the order $X = NH_2 < SCH_3, OCH_3, COOH < CN < SH < OH < I, Br, Cl$. Quantitative predictions from the CI spectra are, however, often thwarted by the fact that heterolysis of $[MH]^+$ ions overlaps with heterolysis of $[ME]^+$ adducts. For example, $[C_6H_{11}]^+$ is formed from protonated cyclohexanol in chemical ionization with $i\text{-}C_4H_{10}$, but also in part by the decomposition of $[M(C_4H_9)]^+$ ions by loss of H_2O or C_4H_9OH, respectively[36].

$$[R{-}X{-}H]^+ \rightarrow [R^+] + H{-}X \quad (s)$$

Heterolysis of C—X bonds in onium ions can be considered along with the subsequent fission of further C—C bonds, as can occur under special conditions in (formal) carbenium ions. Examples of this special case of heterolysis (usually referred to as β-cleavage) are provided by the $CI(CH_4)$ analysis of the photodimers *(12)* and *(13)* of cyclohexenone (Scheme 3), as reported by *Field et al.*[37]. An abundant $[MH]^+$ ion is observed for both isomers, but only *(12)* gives an intense $[M/2+H]^+$ fragment *(14)*. It is assumed that *(12)* decom-

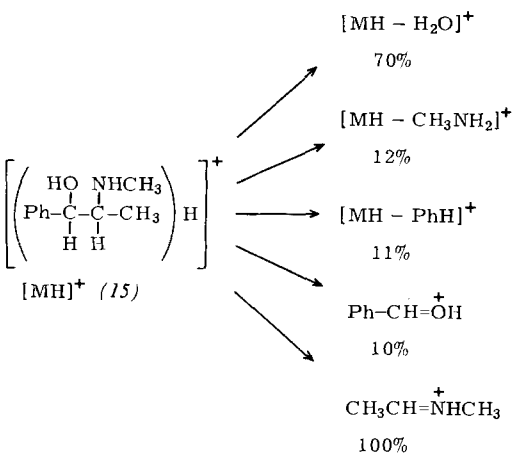
[*] An attempt at a detailed classification is given in [7j].

poses promptly to *(14)* by double β-cleavage *via* a β-oxocarbenium ion *(12a)* as an intermediate; with *(13)* an analogous genesis is likely to be quenched at this intermediate stage, since the corresponding α-oxocarbenium ion *(13a)* represents an energetically unfavorable intermediate. This case illustrates how chemical ionization permits constitutional isomers to be readily differentiated. As in this very example, this is often not possible on electron-impact ionization.



Scheme 3. Different CI fragmentations of constitutionally isomeric photoproducts *(12)* and *(13)* from 2-cyclohexen-1-one. Reagent gas: CH_4.

When several functional groups are available for protonation a certain multiplicity of fragments may result from the parallel occurrence of various possible heterolytic processes; frequently, this multiplicity reflects the gross structural features of the substrate more evenly and completely than is the case with electron-impact ionization, in spite of the latter's numerous competitive and consecutive fragmentation paths. An illustrative example is provided by a simplified consideration of the competing primary heterolyses of ephedrine (Scheme 4) (these are actually likely to proceed in a more complex manner, presumably because of neighboring group participation; cf. Section 3.1.5)[38].



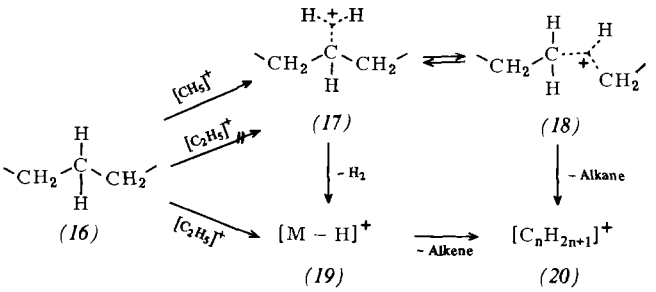
Scheme 4. CI fragmentation of ephedrine: diverse reactions as a consequence of protonation at different sites. Reagent gas: CH_4.

3.1.3. Rearrangements

This type of reaction, more complex than the preceding ones, arises formally from the combination of bond cleavage with bond formation. An intermolecular variety of H-rearrangement can again be encountered in substrate ionization, effecting the usual proton transfer by Brønsted acids [eq. (i) and (j)]. Abstraction of a hydride ion by Lewis acids [eq. (t)] can be regarded, in a way, as its counterpart. This latter process is often considered as a primary ionization event along with protonation and adduct formation, although, according to their masses, the resulting $[M-H]^+$ ions already represent fragments; moreover, it is not immediately possible to differentiate hydride abstraction from decomposition of short-lived $[MH]^+$ ions (cf. Section 3.3.1) through loss of H_2, *i.e.* from a true fragmentation process.

$$[C_2H_5]^+ + R{-}H \rightarrow [R]^+ + C_2H_6 \qquad (t)$$

It was shown by an ion cyclotron resonance (ICR) experiment[*][39a–39c] that both hydride abstraction *and* H_2-loss from $[MH]^+$ ions take place in the chemical ionization of alkanes with CH_4 as reagent gas. The study revealed that $[C_2H_5]^+$ reacted exclusively as a hydride-acceptor as in eq. (t), and not as a proton donor according to eq. (j) (which would be possible on thermodynamic grounds). In contrast, $[CH_5]^+$ was, however, found to furnish extremely unstable carbonium ions *(17)* and *(18)* by protonation of the alkane *(16)* (Scheme 5); these ions decompose quantitatively with



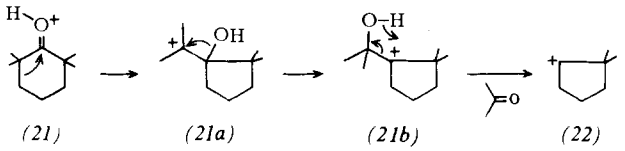
Scheme 5. CI fragmentation of *n*-alkanes with partial structure *(16)*.

loss of H_2 or smaller alkane molecules ("dissociative ionization"[7a]) to yield $[M-H]^+$ *(19)* and various $[C_nH_{2n+1}]^+$ ions *(20)*. At the same time, the alkyl ions *(20)* also arise from *(19)* by (formal) loss of alkene molecules, presumably as a result of β-cleavage (cf. Section 3.1.2); extensive C/H rearrangements precede this terminal step[30].

The fact that in the protonation of C—C and C—H bonds [*(16)→(17), (18)*], and also in hydride abstraction [*(16)→(19)*] the attack by $[CH_5]^+$ or $[C_2H_5]^+$ occurs largely statistically at every bond (random-attack concept)[6], causes saturated hydrocarbons to undergo a multiplicity of competing degradation reactions, which is unusual for chemical ionization. This more or less E1-like variety of fragmentation processes is in distinct contrast to the behavior of functionalized molecules (*e.g.* RX in Section 3.1.2); in these the primary ionization process is governed by ion/dipole interactions, causing a strictly localized attack of the reagent ion and thus correspondingly localized subsequent decomposition.

[*] In the case of competing reaction channels, it is possible to show conclusively which products of ion/molecule reactions arise from which ionic precursors by performing a double resonance experiment. As an integrating method of measurement mass spectrometry with conventional chemical ionization cannot disclose individual processes; for a review cf. [39d, 39e].

The chemistry of carbenium ions in solution leads one to suspect that in chemical ionization, too, intramolecular rearrangements will neither be rare nor be limited to H-transfer. With unlabeled compounds, skeletal rearrangement is usually hard to spot unless it involves rearrangement of groups containing hetero-atoms whose dislocation is readily apparent from fragment mass or competition. This applies, for example, to the CI(CH_4)-induced decomposition of 2,2,6,6-tetramethylcyclohexanone. The $[MH]^+$ ion *(21)* of this compound, formally corresponding to a carbenium ion, undergoes



(21) *(21a)* *(21b)* *(22)*

Scheme 6. CI(CH_4)-induced skeletal rearrangements of the Wagner-Meerwein type in cyclohexanone derivatives with a high degree of α-alkylation.

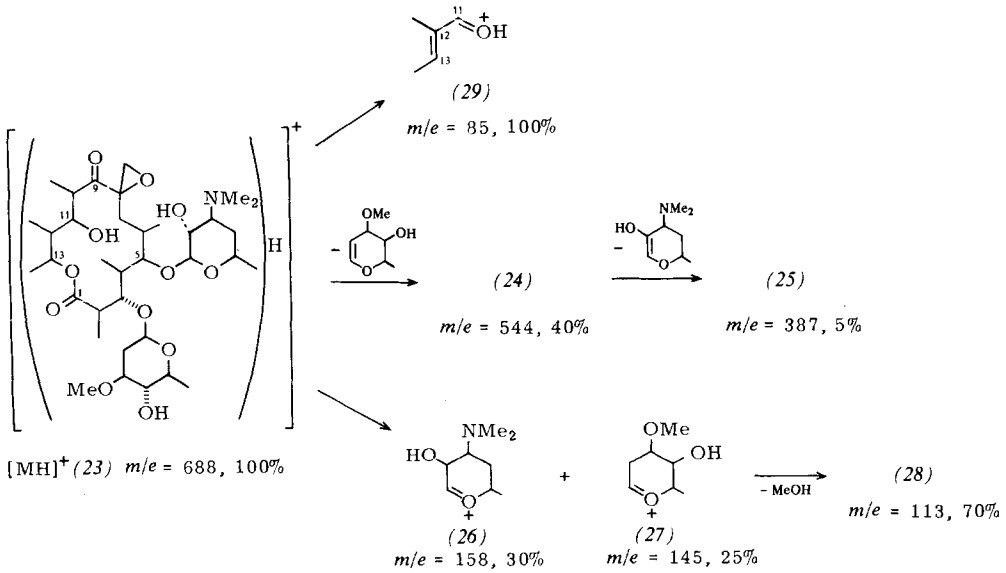
a dominant fragmentation process in which acetone is ejected as a neutral particle; this can be plausibly explained by ring contraction to *(21a)* with subsequent migration of the hydroxyl group [*(21a)*→*(21b)*] (Scheme 6). In *cis*- and *trans*-2,6-dimethylcyclohexanone the analogous process can likewise be observed, though with ejection of acetaldehyde being much less pronounced[40].

3.1.4. Elimination Reactions

In chemical ionization, elimination reactions have in common with heterolyses that saturated or unsaturated neutral particles are lost from ionized substrate. However, elimination is more complex in that bond rupture is formally combined with intramolecular rearrangement. The rearranged entity is often an H atom. In heterolysis [eq. (s)] the neutral molecule to be lost is already present as a leaving group: in elimination this neutral molecule must first be formed in a reactive intermediate or transition state.

We have encountered examples of elimination reactions in the preceding sections. The methoxymethyl esters *(2a)* and *(2b)* decompose after protonation following elimination routes, by way of *(4)*, and not by heterolysis *via (3)*. In the decomposition of $[MH]^+$ ions *(7)* the heterolysis to *(10)* is only the "high-temperature" path; under milder conditions elimination becomes prevalent in this case as well. In the decomposition to *(8)* and *(9)*, elimination processes even occur in two ways (1,1- and 1,2-elimination). In general, eliminations (like heterolyses) are of great diagnostic value for structural analysis; in useful extension of EI fragmentation, they frequently disclose several elements of the overall structure simultaneously rather than spotlighting one particular detail. Since protonated hetero-atoms (onium centers) often provide similarly favored reaction sites, substituents at these centers are mostly better recognized in CI than in EI spectra; in the latter, one single cleavage process may dominate fragmentation entirely. This is illustrated by the CI(i-C_4H_{10})-induced decomposition of the macrolide antibiotic oleandomycin (Scheme 7)[7g]. By elimination processes the protonated molecule loses both sugar constituents in succession [*(23)*→*(24)*→*(25)*]; thereby not only these moieties are disclosed but also the intact macrolide ring as the structural core. Heterolyses of the protonated glycosidic bonds yield the oxonium ions *(26)* and *(27)*, thus providing valuable complementary findings. A diagnostically especially important fragment is *(29)*: it is formed by elimination (opening of the lactone ring in a manner similar to a McLafferty rearrangement) and, after protonation of the carbonyl group in position 9, by heterolytic β-cleavage (similar to a retroaldol fission). This process also occurs with other macrolides containing a 14-membered ring, *e.g.* with erythromycin B[7g], from which an ion with $m/e=99$ results due to the presence of a 13-ethyl substituent. This fragment is thus suitable for an approximate localization of substituents within the ring section encompassed (C-11 to C-13). Decomposition of these compounds on electron impact is characterized by complete disintegration of the basic structural units; only residual structures of the amino-sugar components are recognizable (due to the strong fragmentation-inducing effect of the Me_2N substituent).

Analogously, a direct insight is often obtained into the way subunits are linked in oligomeric molecules, as is often revealed



Scheme 7. CI(i-C_4H_{10})-induced heterolyses and elimination reactions in oleandomycin.

only by extensive chemical degradation. The CI-fragmentation of peptides can serve as an example representative of many other potential applications to the analysis of natural products (*e.g.* nucleosides[41] or oligosaccharides[42]). The principal advantage of chemical ionization over electron-impact ionization for peptide-sequence analysis—a classical[43] and yet also recent[44] objective of mass spectroscopy—lies in the fact that both *N*-terminal ions and *C*-terminal ions are produced simultaneously [eq. (u)][45]. Unless very special derivatization is employed[*], electron-impact ionization affords only ions of the former kind.

$$[(R{-}\underset{\underset{O}{\|}}{C}{-}NH{-}R')H]^+ \rightarrow [R{-}C{\equiv}O]^+ \text{ and } [H_3N{-}R']^+ \qquad (u)$$

In CI, the *C*-terminal ammonium ions are thereby formed by elimination (ejection of a neutral aminoketene molecule); for the genesis of the *N*-terminal acylium ions the question of involvement of elimination or heterolysis (cf. Scheme 1) remains unresolved. Since, in principle, protonation can occur at every single peptide bond, two series of fragments are produced which, owing to the redundancy of their information, should permit the deduction of the amino-acid sequence even when isobaric fragment ions interfere. Thus, there is little need to resort to high-resolution mass spectrometry.

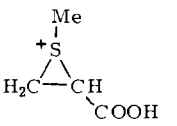
3.1.5. Substitution Reactions

According to the formalism used, substitution reactions in chemical ionization consist of a combination of two simple steps: the displacement of a leaving group in the substrate by a nucleophile amounts to a heterolysis associated with the addition of the nucleophilic reagent [eq. (v)]. As outlined in Section 3.1.2, in a substrate of type RX the formation of potential leaving groups is a direct consequence of ionization at X. Depending on the external or internal origin of the nucleophile Y: (reagent gas or functional groups within the substrate), again an intermolecular and an intramolecular mode (S_N2 or S_Ni type) are conceivable.

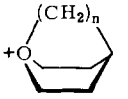
$$Y: + [R{-}X{-}H]^+ \rightarrow [R{-}Y]^+ + H{-}X \qquad (v)$$

It is uncertain whether direct intermolecular substitution, *i.e.* a process corresponding exactly to the S_N2 type, plays a role in chemical ionization [eq. (p) and Section 2.3]. In their net results, occasionally observable hydrolyses like those of trimethylsilyl and perfluoroacyl derivatives on use of H_2O or other insufficiently dried reagent gases, fall into this category, as do the ammonolyses[46] and transesterification reactions[47] of esters on use of NH_3 or CH_3OH. However, detailed investigation of such reactions of the ionized substrates with the reagent gas itself, *e.g.* the hydrolysis of aliphatic dimethyl α,ω-dicarboxylates in dependence on the number of carbon atoms in the chain (3—12)[47], compel one to assume more complex pathways, namely elimination of HX from $[RXHY]^+$-adducts with neighboring group participation by the second ester group instead of direct HX/Y-substitution in $[RXH]^+$ ions.

In contrast to this intermolecular mode, intramolecular substitution in chemical ionization is relatively well documented. S_Ni reactions are reflected, for example, in protonated open-chain bifunctional molecules in heterolytic processes that are absent or unimportant in monofunctional analogs under comparable conditions. $[MH]^+$ ions of simple amino acids, for instance, undergo no appreciable ejection of NH_3, in sharp contrast to those containing additional functionalities; thus, *S*-methylcysteine is readily converted into a cyclic sulfonium ion *(30)* by an S_Ni reaction[48]. Analogous reactivity was observed with a series of polyamines under CI conditions[49], which is paralleled by their EI behavior[50]. The formation of bicyclic oxonium ions of structure *(31)* must be interpreted along similar lines[51].

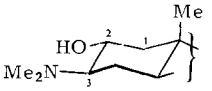


(30)

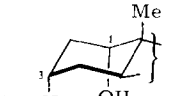


(31), n = 1, 2

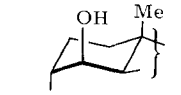
More direct indications of interactions of the S_Ni type can, of course, be expected for stereochemical effects[52a]. Marked reactivity differences may thus be exhibited by polyfunctional alicyclic systems, depending on the spatial arrangement of the substituents. An elegant study of 1,3-, 2,3-, and 3,4-difunctionalized steroidal amino alcohols was reported by *Longevialle et al.*[52b]. These authors found that in all compounds in which intramolecular H bridges between the substituents were sterically possible [*e.g.* in *(32)* and *(33)*], there was no ejection of H_2O from $[MH]^+$; such ejection was prominent when the leaving group was not hydrogen-bonded and S_Ni attack was configurationally favored [*e.g.* in the 3,4-diaxial or 1,3-equatorial/axial *trans*-compounds *(34)* and *(35)*]. Furthermore, proportions of specific conformations of the protonated forms were estimated from the $[MH]^+/[MH-H_2O]^+$ ratio. The results showed surprisingly good agreement with IR-spectroscopic measurements.



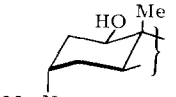
(32)



(33)



(34)

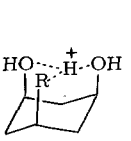


(35)

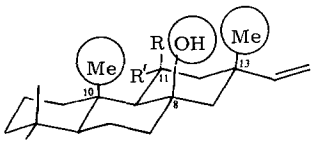
The fact that H-bond formation in bifunctional molecules (cf. Section 3.1.1) can also block sterically unhindered S_Ni reactions follows from investigations of open-chain compounds. In the $CI(CH_4)$ spectrum of *n*-decanol, $[MH]^+$ ions are completely missing, mainly due to the loss of H_2O[6]; in the $CI(CH_4)$ spectrum of 1,10-decanediol *(11)*, X = OH, $n = 10$, the $[MH]^+$ ions retain as much as 60% relative intensity[33].

[*] Reduction of the polypeptide chain to polyamino alcohols by *Biemann*'s method [43, 44] with $LiAlH_4$ intentionally generates optimum conditions for a uniform formation of *C*- and *N*-terminal fragments.

As shown by investigations of alicyclic diols and triols[53], alkyl effects play an additional role. In general, in compounds of the type *(36)* the loss of water from $[MH]^+$ is quite



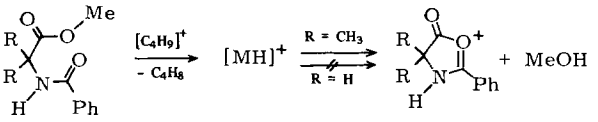
(36)



(37), R = OH, R′ = H (11β-OH)
(38), R = H, R′ = OH (11α-OH)

sensitive to the configuration of the group R. For the $[MH]^+/[MH-H_2O]^+$ ratio, the case R = OH provides the upper and $R=CH_3$ the lower extreme value. Alkyl effects may prevent the formation of linear H-bonds for example in the diterpenediols *(37)* and *(38)*; this effect may be so marked that the spatial arrangement of the hydroxyl groups is no longer of importance for the extent of loss of water[54]. Apparently, the space-filling by the 10β- and 13β-methyl groups of *(37)* precludes the formation of such a bridge; in *(38)* it is ruled out in any event for configurational reasons. Indirectly, cooperative effects of this type may also be of importance for the behavior of open-chain compounds.

As a result of a geminal dialkyl effect[55], the ejection of methanol from the $[MH]^+$ ions of, *e.g.*, α-(benzoylamino) acid methyl esters is strongly dependent on additional α-substitution: in *(39)* the amount of loss of CH_3OH is considerable (25% relative intensity, $[MH]^+$ = base peak), in *(40)* it is not even detectable[56] (Scheme 8).



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

(41)

Scheme 8. Loss of CH_3OH from protonated α-benzoylamino acid methyl esters in dependence on α-alkylation (alkyl effect).

4. Instrumental and Methodological Aspects

4.1. Instrumentation for Chemical Ionization

As far as instrumental aspects are concerned, the only essential difference between chemical ionization (CI)[*] and electron-impact ionization (EI) lies in the manner in which ions are produced. Mass separation and detection are based on the same principles in both techniques. Conventional EI mass spectrometers can thus be modified for CI or combined EI/CI operation[**] with little effort. No loss of resolution was observed for high-resolution instruments adapted to CI operation[59, 71]. Modifications are required (they are already taken care of in commercial instruments) to allow the ion source to be operated at a working pressure of around 1 mbar (in EI instruments *ca.* 10^{-6} mbar) through fairly gas-tight construction[*]; suitably high pumping capacities have to maintain the necessary minimum vacuum (10^{-4} to 10^{-5} mbar) outside the ion source for operation of a heated cathode[**] as well as in the analyzer to avoid collisions of ions with residual gas. Pump performances of 600 to 1200 $l \cdot s^{-1}$ at the source housing and differential pumping of the analyzer are thus necessary. In magnetic field instruments, in which the ion source is held at high potentials (acceleration voltage in the kV range), precautious must also be taken for electrical insulation of the reagent gas, which will become conducting at the prevailing pressures[7i, 7k, 59]. The technical simplicity of chemical ionization is also borne out by the fact that the same sample-introduction techniques are used for analysis of single substances as in electron-impact ionization. As in EI, in CI mass spectrometry the combination with gas chromatography (GC) leads to a major broadening of the scope of the technique, since analyses of complex mixtures become possible (cf. Section 5.1).

Technically, combination of gas chromatography with CI mass spectrometry is simpler than that with its EI counterpart—at least as far as the level of performance of monogas systems[58, 63, 64] is concerned. The reagent gas, usually CH_4, can be passed through the gas chromatograph and thus serve at the same time as a carrier gas. Because of the "high" pressure required in the ion source, molecular separators or split systems become unnecessary, *i.e.* can be replaced in favor of direct connections which operate largely without loss of sample and with minimum failure and maintenance requirements[58, 63]. Gas chromatograms are obtained by recording total ion current (TIC) representative of the sample[***]. Independent optimization of separation and reagent gas properties is made possible in the dual gas concept[****] by which different carrier and reagent gases are employed. In order to avoid interference with the separation process, the reagent-gas is admixed with the carrier gas flow only shortly before entering the ion source[65–68]. On introduction of capillary-GC/CI mass spectrometry with typically low carrier gas flows (*ca.* 1 ml/min) relative to that of reagent gas (20 to 30 ml/min) this concept could be realized in its "purest" form, *i.e.* without compromising the versatility of CI operation by major carrier gas contributions (Fig. 2)[65, 67–70].

For packed columns with considerably higher carrier gas flow (30—50 ml/min) either the carrier gas (noble gas, N_2)

[*] Since the working pressure is significantly higher in chemical ionization than in electron-impact ionization, the term "high-pressure" ionization is occasionally used.

[**] In principle, every CI source becomes an EI source as soon as the flow of reagent gas is interrupted. Unless special modifications are made [57] the sensitivity in the EI mode considerably decreases, however, because of the smaller aperture dimensions. The simultaneous or alternative operation of a combination of an independent CI and EI source has been advocated [58], and at least one such dual source is commercially available.

[*] The number and the dimensions of the source apertures into the housing are much smaller than in EI sources. The electron entrance and ion exit apertures have together an area of only 1—2 mm^2.

[**] For primary ionization of the reagent gas other principles than the customary emission of thermal electrons are available (corona discharge, use of radioisotopes such as ^{63}Ni). Plasmas of aggressive reagent gases (*e.g.* O_2, NO) are produced by gas discharge [60—62].

[***] The total ion current (TIC) signal cannot be sampled before mass separation, as is possible in GC/EIMS under certain conditions (helium as the carrier gas, 20 eV ionization energy), since it is predominantly due to unused reagent ions. In dynamic spectrometers, total ion current representative of the sample can be conveniently obtained after mass separation by integrating the single ion currents over preselected mass ranges, *i.e.* with exclusion of reagent ions, in rapid scan cycles (0.1 s). In magnetic field instruments this is less easily achieved.

[****] First described for (non-chromatographic) direct analysis [63].

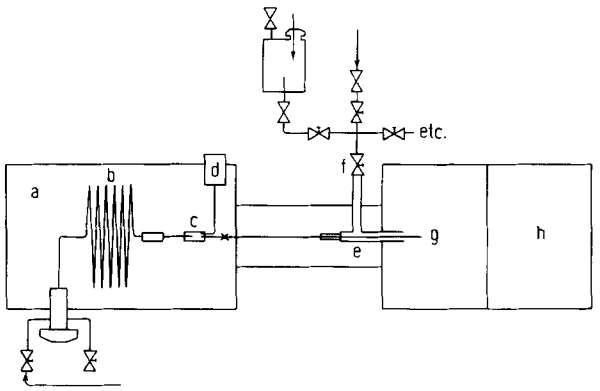


Fig. 2. Block diagram of a GC/CIMS system in typical dual gas operation (cf. [71]). Principal components: a) gas chromatograph with Grob injector, b) capillary GC column, c) split systems for dual FID/TIC recording, d) flame ionization detector (FID), e) coaxial interface, f) reagent gas inlet, g) mass spectrometer, h) dedicated computer.

is modified[*] in the desired manner by addition of appropriate amounts of a reagent gas (*e.g.* i-C_4H_{10} or NO)[66], or most of it is removed in molecular separators or flow dividers before the reagent gas is added. In the former case the full sensitivity of the system is retained at the expense of some flexibility in the choice of the CI conditions[**]; in the latter case complete flexibility of the experiment is retained as in capillary-GC/CI mass spectrometry, yet at the expense of sensitivity owing to unavoidable losses of material on pressure reduction.

4.2. Methods of Chemical Ionization

4.2.1. Choice of the Reagent Gas

The choice of the reagent gas is of decisive importance for the achievement of the analytical purpose. This choice determines not only the type of ionization (redox or acid/base type)[***], but also the exothermicity of the ionization process. As noted before, these two factors largely shape the information to be derived from the CI spectrum. According to the magnitude of the difference (Δ) between the recombination energy or the proton affinity of the reagent gas and the substrate, the result will range between extremes of high ionization selectivity, reduced fragmentation, and thus low substrate specificity (low Δ value) on the one hand, and high substrate specificity, extensive fragmentation, and low selectivity as a result of universal ionization (large Δ value) on the other. Control of selectivity and fragmentation is important not only for the analysis of multicomponent systems, in which it allows discrimination of disturbing components, but also for structural analyses of isolated, single compounds that contain several functional groups distinguished by different proton affinities[70, 15c].

In this connection it is worth mentioning experiments with binary reagent gas systems, including partially modified systems (addition of modifying gas $<10\,\%$)[15d] such as Ar/H_2O[15a], He/H_2O[15b], and many others[15d]; mild protonation is generally used to provide stable $[MH]^+$ ions, while strongly exothermic charge exchange[14b] produces highly reactive $[N]^{+\bullet}$ ions that decompose very much in an EI-like fashion. In this way one attempts to combine the advantages of chemical ionization with those of electron impact (cf. also Fig. 1). In single-compound analysis there may be real advantages to such a "hybrid" concept; in the analysis of complex mixtures by GC/CIMS, however, a sequential approach by independent, yet correlatable[71] single experiments with only one reagent gas at a time (a "puristic" concept) may frequently be preferable[65, 67, 70, 100].

4.2.2. Selected Ion Monitoring

This recording technique, which was initially developed and proposed for EI mass spectrometry under the name of "mass fragmentography"[72][*], has today acquired similar importance for CI mass spectrometry, especially in GC/CIMS analysis. In this technique the usual recording of complete spectra (*i.e.* repetitive scanning of wide—largely empty—mass ranges) during a separation process (*e.g.* fractional evaporation or GC/MS) is abandoned; instead, during the same period of time only a few selected masses are monitored continuously by rapid switching rather than sweeping electric or magnetic fields. Thus, for these few ions deadtimes are reduced by several orders of magnitude, with the result that detection limits are lowered dramatically from the nanogram down to the lower picogram level (some 10^{-12} g). Since this detection principle is independent of the mode of the ion production, it lends itself immediately to GC/CIMS analysis.

5. Analytical Applications

5.1. Analysis of Organic Compounds

This Section intends to point out applications of chemical ionization that are characteristic of both the analytical objective (determination of structure, identification, detection, quantitative determination) as well as of the fields in which it is chiefly applied (biomedical field, environmental sciences). For more complete presentations the literature should be consulted[1b, 7n].

Of the advantages CI may offer over EI mass spectrometry for analytical purposes reliable molecular weight information and the possibility of controlling fragmentation are of prime importance. This is true not only for structural analysis but also for the identification of known, yet unexpected compounds present as minor components in mixtures. The detection and quantitative determination of expected, known compounds in the presence of unknown constituents or ballast material may likewise profit from control of fragmentation behavior. Pronounced $[MH]^+$ ions and deliberately suppressed frag-

[*] Addition of approximately 10 % reagent gas to the carrier gas [15d] usually suffices to moderate the latter's "hard" charge-exchange (CE) character (addition of NO), or to modify it to a CI reagent (addition of i-C_4H_{10}).

[**] In this case, the carrier gas serves only as an inert collision gas [63], which is essential to maintain CI conditions.

[***] Depending on the substrate (differences between recombination energy and proton affinity), one reagent gas can act both ways simultaneously: in the typical acidic CH_4 plasma $[C_2H_4]^{+\bullet}$ and $[C_2H_5]^+$ ions are potential charge-exchange (CE) reagents [7j].

[*] After considerable terminological uncertainty [74] (the synonyms "multiple ion monitoring", "multiple ion detection", "selective ion recording", "specific ion plotting" and many more were in use; cf. also [73a]) the acronym SIM ("selected ion monitoring") seems to have found wide acceptance [73].

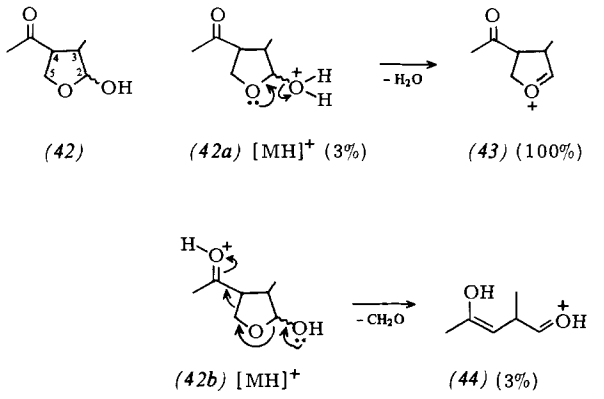
mentation are, of course, important non-instrumental prerequisites for high detection sensitivity, as is essential in trace analysis since they reduce the risk of spectral interference by foreign substances (which will also fragment to lesser degrees, and hence be more readily detected than in EI mass spectrometry). The ease of suppressing interferences, the greater reliability in qualitative applications, and the higher accuracy in quantitative work by measurement in the less disturbed region of highest possible mass (thus excluding systematic errors) are direct advantages. The control of ionization also results in great flexibility as to the selectivity desired; its optimization frequently permits the complete exclusion of disturbing accompanying materials from ionization, and thus a reduction of background in favor of lower detection limits. In these respects, electron-impact ionization is rather inflexible[*].

Finally, in structural analysis and identification, the great versatility of chemical ionization allows for the use of a series of reagent gases, in order to probe, step by step, for specific structural evidence[70]. This extension to multiple analyses of one and the same sample is certainly justified in the analysis of complex mixtures by GC/CI mass spectrometry; the expenditure of work is then economized when the structural characterization of more than only a few compounds is required, and when difficult problems of correlation can be avoided by keeping the GC parameters constant[65,67,70,71] throughout the series of GC/CIMS runs. It also has to be kept in mind that other ways are currently unavailable if one attempts to compensate for the lack of structural information otherwise provided by other spectroscopic means.

5.1.1. Elucidation of the Structure of Unknown Compounds

Chemical ionization, like electron-impact ionization, will frequently allow solution of only part of a complex structural problem. In any case, its most likely minimum contribution will be the determination of the molecular weight and, when using high-resolution instruments, the determination of the elemental composition. This information alone is especially valuable because of its high reliability[**]. However, the greater simplicity and better predictability of CI fragmentation, which is often complementary in character to that of EI mass spectrometry, and in particular its better correlation with structural elements will make its extensive evaluation highly attractive in structural work. Little effort has as yet been made in exploiting this feature in practice.

The situation is illustrated by the determination of the constitution of the antibiotic botryodiplodin *(42)* (Scheme 9). In view of the poor reproducibility of the EI behavior of the compound (tautomerizable five-membered ring lactol structure with an anomeric center at C-2), recourse was made

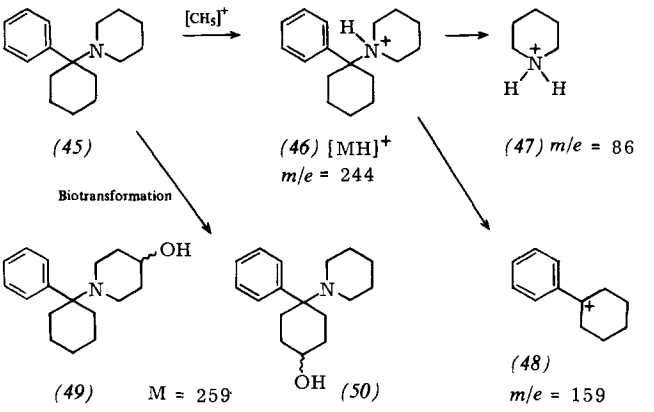


(42) *(42a)* $[MH]^+$ (3%) *(43)* (100%)

(42b) $[MH]^+$ *(44)* (3%)

Scheme 9. CI(CH_4)-induced decomposition of botryodiplodin *(42)*.

to chemical ionization[76] (incidentally, this was the first application of CI to structure analysis). Although the intensity of the $[MH]^+$ ions was relatively low due to excessive decomposition of *(42a)* into *(43)*—(as usual at that time, methane was used as the reagent gas) the molecular weight and empirical formula could be determined. Indication of a β-oxygenated carbonyl system with no substituent at C-5 was afforded by the loss of $CH_2{=}O$ from the $[MH]^+$ ion [*(42b)*→*(44)*]. This type of fragmentation is similar to the retroaldol decomposition of oleandomycin [*(23)*→*(29)*, Scheme 7]; since double β-cleavage occurs, it can also be considered as a Grob fragmentation[77] in the gas phase[78,79]. From the above and the results of ^{1}H-NMR analysis, structure *(42)* was finally arrived at in which only the stereochemistry at C-3 and C-4 remained unestablished.



(45) *(46)* $[MH]^+$ *m/e* = 244 *(47)* *m/e* = 86

(49) M = 259 *(50)* *(48)* *m/e* = 159

Scheme 10. CI fragmentation and biotransformation of phencyclidine *(45)*. *(45)* with a perdeuterated phenyl group affords an ion with *m/e* = 249 instead of *(46)*, and an ion with *m/e* = 164 instead of *(48)*. *(47)* remains unshifted.

As a result of their small absolute amount and low degree of enrichment, compounds "isolated" from physiological fluids often cannot be subjected to parallel spectroscopic investigations like those used for *(42)*. Structural characterization of drug metabolites is clearly such a case. Work of this kind is admittedly easier than that on natural products because the structure of the starting material is known and the biotransformation is almost invariably confined to the molecular periphery[*]. Determination of the structure of two metabolites

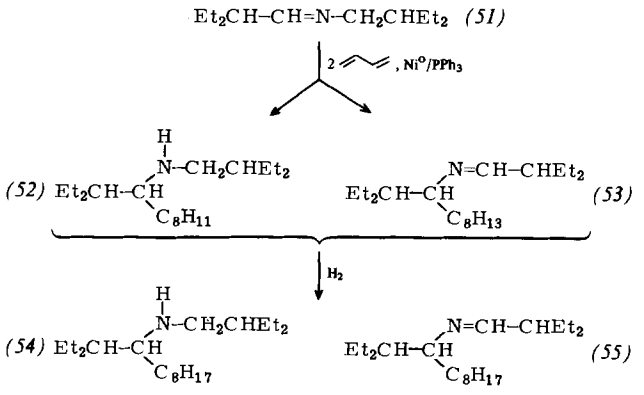
[*] The attempt to achieve selective ionization in EI by reducing electron energy to below the ionization threshold of individual classes of compounds is known to cause a prohibitive loss in sensitivity.

[**] As in the EI method, limitations arise from the necessity to vaporize the sample without thermal decomposition. However, pyrolysis is easier to recognize in CI than in EI spectra, particularly when more than one product, *i.e.* several quasimolecular ions (cf. footnote [*] on p. 436), as is the case with certain quaternary nitrogen compounds [75]. If in this latter case only one pyrolysis product is formed, the presence of a covalent compound can be simulated (*e.g.* in the phospholipid dioleylphosphatidylcholine $ROP(O)(O^-)OCH_2CH_2NMe_3^+$ by intramolecular methylation to the covalent $ROP(O)(OMe)CH_2CH_2NMe_2$ [7g]).

[*] In principle, skeletal changes are not entirely excluded. Cases of ring contraction (7-ring → 6-ring) are known, *e.g.* from the biotransformation of 5*H*-dibenz[*b,f*]azepine-5-carboxamide (carbamazepine) [80].

of the local anesthetic phencyclidine *(45)* can serve as an example (Scheme 10)[81]. GC/CIMS analysis (packed column, monogas system with CH_4 as universal gas) of a silylated crude extract from human urine showed, besides unchanged parent drug *(45)*, two GC peaks whose spectra corresponded to trimethylsilyl derivatives of isomeric monohydroxy metabolites *(49)* and *(50)* ($[MH]^+$: $m/e=332$). Marked losses of trimethylsilanol in both cases ruled out substitution of aryl positions. Comparison of these spectra with the fragmentation of the parent compound [larger structural elements are revealed in a manner typical of chemical ionization: *(45)* → $[MH]^+$ → *(47)* by elimination of phenylcyclohexene; *(45)* → $[MH]^+$ → *(48)* by heterolysis with loss of piperidine] rapidly permitted the substitution region to be narrowed down to one of the saturated rings in both cases. Silylated *(49)* decomposed to silyloxy-*(47)* ($m/e=174$) and unchanged *(48)*, while silylated *(50)* decomposed to silyloxy-*(48)* ($m/e=247$) and unchanged *(47)*. The complementary nature of EI and CI is borne out by the fact that in the EI mass spectra $[M]^{+\bullet}$ ions were much less intense than $[MH]^+$ ions in CI, but that the EI fragmentation allowed an exact placement of the hydroxyl group in one of the two metabolites *(50)*. The structural proposals *(49)* and *(50)* were subsequently confirmed by synthesis.

A similar situation may arise in structural investigations of hard-to-separate reaction mixtures from preparative organic chemistry; admittedly sample sizes are mostly larger and sample compositions less complex than when analyzing biological materials. Although the starting materials are known, the variety and number of the products may be large enough to thwart their isolation and application of conventional methods for structure elucidation or confirmation. As the following example shows, multiple GC/CIMS analysis with variation of the reagent gas[65,67,71] can be of help in such cases. The sample studied originated from a co-oligomerization experiment with butadiene and the Schiff base *(51)* (Scheme 11). Under Ni(0)-ligand catalysis, among other products, 2:1 adducts mainly of the types *(52)* and *(53)*[82] were formed.



Scheme 11. Co-oligomerization of 1,3-butadiene with the Schiff base *(51)* under nickel(0)-ligand catalysis with subsequent hydrogenation.

Figure 3[83] shows the gas chromatogram of a distillation fraction after (incomplete) hydrogenation to *(54)* and *(55)*. The difficult separation of the components 3/4 and 5/6 required the high resolution of glass capillary columns in the GC/CIMS experiments. Gross structural characterization of the important components sufficed for an evaluation of the oligomerization experiments, and was achieved by employing the reagent gas sequence $CH_4/i\text{-}C_4H_{10}/CH_3OD$. Isobutane invariably gives $[MH]^+$ ions as the base peaks and thus reveals molecular weights, which are hard to obtain by electron-impact ionization in the case of secondary aliphatic amines *(54)*. Methane,

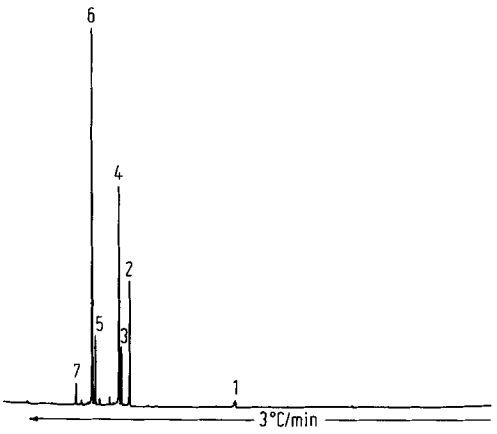


Fig. 3. CI(CH_4)-total ion current-gas chromatogram (TIC-GC) of a partially hydrogenated reaction mixture obtained by co-oligomerization of butadiene with the Schiff base *(51)* under Ni(0)-ligand catalysis (glass capillary column, 20 m × 0.3 mm, SE-54). Components of the mixture: 1) $H_2NCH(C_8H_{17})CHEt_2$, 2) and 3) $Et_2CH{-}CH{=}N{-}CH(C_8H_{17})CHEt_2$ *(55)*, 4) $Et_2CHCH_2NHCH(C_8H_{17})CHEt_2$ *(54)*, 5) $Et_2CH{-}CH{=}N{-}CH(C_8H_{13})CHEt_2$ *(53)*, 6) $Et_2CH{-}CH{=}N{-}CH(C_8H_{15})CHEt_2$, 7) $Et_2CHCH_2NHCH(C_8H_{15})CHEt_2$ (see Scheme 11).

besides confirming the $[MH]^+$ findings, furnished distinct structural information based on fragmentation similar to that of electron-impact ionization: pronounced $[M-H]^+$, $[M-C_5H_{11}]^+$, and $[M-C_8H_{17}]^+$ ions indicate which substituents occupy α-positions with respect to the N atom in the secondary amines and Schiff bases. CH_3OD, like D_2O[84], is an efficient reagent gas for the determination of the number of exchangeable H atoms (two in component 1, one in 4 and 7, none in 2, 3, 5, and 6); in the present case it serves as a probe for the recognition and distinction of primary and secondary amines in the presence of Schiff bases[69,85].

5.1.2. Identification and Detection of Known Substances

A certain minimum of structural characterization is normally required when there is no specific clue as to the identity of the compound in question, *i.e.* there is only an indication of the class to which the compound belongs. If additional complications arise from hard-to-separate mixtures, from a low degree of enrichment, or from small sample quantities, then, for reasons given above, chemical ionization will be the method of choice.

The widespread abuse of drugs provided a challenge to the exploratory application of the new technique for the identification of these materials in clinical analysis. Direct sample introduction, applied to crude extracts of gastric contents, urine, or blood was performed at the National Institutes of Health by a group centered around *Fales* and *Milne* some years ago, as a means of simple rapid screening[*][88]. The

[*] The potential of GC/MS for this field was clearly recognized [86], but instruments then available operated relatively slowly and were generally reserved for non-routine problems [87].

procedure consisted in taking a series of CI(i-C_4H_{10}) spectra during evaporation of the sample and searching them for $[MH]^+$ ions[*]; visual comparison ($[MH]^+$ as search parameter) against the 48 reference spectra then available made it possible to identify rapidly at least the most often abused drugs. The spectrum of a gastric extract (Fig. 4) illustrates an overdose case in which five constituents [*(56)—(60)*]

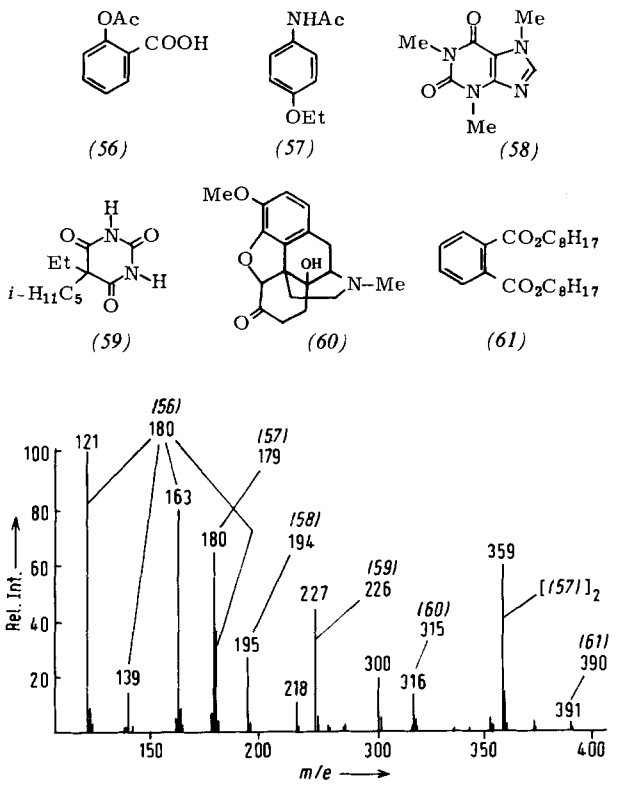


Fig. 4. CI(i-C_4H_{10}) spectrum of an extract of gastric contents after drug abuse (overdose of Percodan). *(56)*, acetylsalicylic acid (aspirin); *(57)*, phenacetin; *(58)*, caffeine; *(59)*, amytal; *(60)*, oxycodon; *(61)*, dioctyl phthalate.

of the preparation Percodan, even in spite of pronounced fragmentation of one component [aspirin *(56)*], could be identified[88]. While contaminants, *e.g.* the ubiquitous dioctyl phthalate *(61)*, barely interfere, the formation of cluster ions of the type $[M_2H]^+$ (cf. Section 3.1) by phenacetin *(57)* is to some extent a disadvantage; cluster formation of this kind is a consequence of high momentary sample pressure which is not always easy to avoid, yet fortunately readily recognized.

In forensic medicine common "street drugs" and narcotics such as heroin can be similarly identified by direct analysis of the confiscated material as such[89]. Diluents and current "narcotic substitutes" are simultaneously identified, and this often enables the investigating authorities to draw conclusions as to the origin of the material[**].

In the past years the increasing spread of technically more sophisticated GC/MS/computer systems, and the resulting automation of spectra comparisons, have replaced much of the initial skillful improvisation in this field. Importance still attaches to direct analyses in cases in which thermal lability or low volatility excludes the use of GC/MS analysis in spite of derivatization. Examples are the identification of LSD[90], or of explosives for which chemical ionization with H_2O as reagent gas has proven valuable[91]. The general trend toward automated identification is reflected in the inclusion of CI spectra in larger general collections of mass spectra, and also in the growth of specific collections of CI reference spectra for drug identification to currently 450 compounds (including the main metabolites and customary associated substances)[92]. An approach developed at the Batelle Institute in Columbus, Ohio, is based on a GC/CIMS analysis of crude extracts; a monogas system operating with packed GC columns and methane as the carrier/reagent gas is used[90, 92]. For compounds of equal molecular weight (which serves as the main search parameter) fragmentation provides sufficient distinguishing criteria. Because of the dependence of CI fragmentation on experimental parameters, strict standardization of the conditions is, of course, necessary.

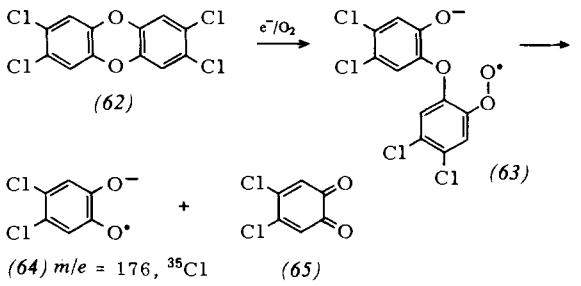
Detection sensitivities very much greater than in the preceding examples are required for analyses of trace components, while at the same time, high substance specificity must be maintained. This applies particularly to the detection of trace components in very complex mixtures. A breakthrough in this direction (detection limits in the lower picogram range and less) was achieved by the technique of selective ion monitoring (SIM), described in Section 4.2.2[72]. A result of general interest, relying on this technique, is the detection of traces of nicotine in the urine of non-smokers[93]. This analysis, which required an extremely high detection sensitivity and very narrow selectivity of ionization, was performed by *Horning et al.* These authors developed a special version[94, 95] of chemical ionization using reagent gases at atmospheric pressure (API) in an "open" ion source; the detection limits of such a system are in the upper femtogram range (1 fg = 10^{-15} g). In a typical experiment a benzene extract of the urine is injected directly into the source flushed with N_2 at atmospheric pressure, and the solvent vapor also acts as a highly selective CE reagent gas ($[C_6H_6]^{+\bullet}$ ions). The presence of nicotine in urine was evidenced by the SIM profile of $m/e = 162$ ($[M]^{+\bullet}$). Surprisingly, the alkaloid was also detected in the urine of all *non*-smokers tested: the nicotine levels of these apparently "passive smokers" were *ca.* 5% of the average content for smokers examined at the same time.

"Negative chemical ionization" (NCI and NCE; cf. Section 2.1) has opened up some interesting and highly topical possibilities for the detection of traces of special compounds. This applies particularly to 2,3,7,8-tetrachlorodibenzo[1,4]dioxin (TCDD), which recently made the headlines. The molecule of *(62)* is remarkably stable in every respect but, after the formation of a radical-ionic adduct *(63)* with O_2 (reagent gas in a Townsend ion source), it decomposes readily into an ionic fragment *(64)* (Scheme 12).

By means of this fragment, *(62)* can be detected in extremely low concentration (a 2×10^{-12} g sample gave a signal/noise ratio of over 50:1 on the SIM trace[96]) and, owing to the specificity of the process and the relatively low mass of the fragment, can be easily differentiated from other wide-spread

[*] The presence of several $[MH]^+$ ions (*e.g.* when combined preparations were ingested) causes irregular changes of the intensity profiles within a series of subsequently recorded spectra, in contrast to the presence of CI fragments.

[**] For detailed analysis, the GC/CIMS version is, of course, likewise recommended; in this context, the use of He/NO (10/1) as a moderated CE reagent gas has been reported [66].



Scheme 12. Decomposition of 2,3,7,8-tetrachlorodibenzo[1,4]dioxin *(62)* after negative chemical ionization (NCE) with O_2 as the reagent gas.

polyhalogenated compounds which are hard to separate by present techniques.

5.1.3. Quantitative Analysis[*]

Here too, direct introduction of the sample with fractionating evaporation may be of certain interest as the simplest mode of analysis when, for example, only one or a few main components of a simple mixture are to be determined quantitatively. A typical case in which derivatization and GC/CIMS analysis proved hardly worthwhile has been reported by *Fales et al.*[97]. These authors were concerned with the quantitative determination of phenylthiohydantoin (PTH) derivatives of amino acids which they obtained in decreasing purity in the course of a sequential Edman degradation of sperm whale myoglobin, *i.e.* in admixture with PTH derivatives of the amino acids next in the sequence. After identification of all the PTH-amino acids present by means of a preliminary CI run, quantitative determination was successfully achieved by the addition of the corresponding C_6D_5 derivatives in known amounts as internal standards (isotope dilution analysis). This permitted the identification of the chief component in the mixtures obtained at every single step (in contrast to visual inspection of spectra beyond step 20), and thus the deduction of the correct sequence of the protein chain. The concentrations of the PTH derivatives were obtained from the relative intensities of the $[MH]^+$ ions from the sample and standard in the very simple CI(i-C_4H_{10}) spectra.

For quantitative determination of very low concentrations in multicomponent mixtures, GC/MS with the use of selective ion monitoring (SIM) is, of course, much more effective. The GC/CIMS combination is a very promising alternative to GC/EIMS[98] because of the advantages mentioned above, especially the lower susceptibility to interference by material co-eluted with the sample. As in the direct-introduction mode, an internal standard is added in a known amount (depending upon the expected concentrations) to the original medium, *e.g.* blood plasma, before isolation and clean-up (generally by extraction) of suitably enriched fractions. As with the above phenylthiohydantoins, the current practice is to use standards multiply labeled with stable isotopes of high isotopic purity[95b]. Multiply deuterated or ^{13}C-labeled standards with at least 3 amu mass difference from the unlabeled substrate are particularly suitable, because they preclude overlap in the simultaneous recording of selected $[D_0]/[D_n]$ mass pairs even in the presence of the $[MH]^+/[M]^{+\bullet}/[M-H]^+$ peak groups in CI(CH_4) spectra (should CH_4 be unavoidable as reagent gas).

A typical case of pharmacokinetic investigations is the quantitative determination of phencyclidine *(45)* (Scheme 10) (already mentioned in Section 5.1.1) as unchanged parent drug in blood and urine[81]. The derivative with a perdeuterated phenyl group is the internal standard and CH_4 is the carrier and reagent gas (monogas system). As mentioned above, only the two main fragments *(47)* ($m/e=86$) and *(48)* ($m/e=159$) are prominent apart from $[M]^{+\bullet}$ and $[MH]^+$ ($m/e=243$ and 244; relative intensity 100 and 50%, respectively)[*]. Unlike *(48)*, fragment *(47)* contains no heavy isotope in the case of the $[D_5]$-derivative and, thus, cannot be used as a reference mass. The mass pairs $m/e=243/248$ and 159/164 are, therefore, used for selective ion monitoring. The recording of two ions characteristic of the compound, together with practically identical retention of the substrate and the added standard provides sufficient compound specificity and is nearly equivalent to a duplicate analysis by independent routes. Interference at one of the two selected masses (*e.g.* by metabolites) would result in a discrepancy between the two values found.

By establishing two calibration curves for the two selected mass pairs with known amounts ($[D_0]/[D_5]$ intensity ratios are plotted against increasing amounts of the $[D_0]$ compound), the necessary linearity of response is ascertained for the required concentration range; unknown concentrations can then be interpolated directly. The versatility of chemical ionization and its special advantages in the field of pharmacological chemistry are amply demonstrated by a multitude of further reports on the quantitative determination of drugs such as methadone (and its metabolites)[99], phenformin[100], morphine[98], quinidine and lidocaine[101], tolbutamide (and its metabolites)[102], several barbiturates and hydantoins[103], and also of endogenous substances such as purine and pyrimidine bases and nucleosides (as permethylated derivatives)[104].

5.2. Analysis of Inorganic and Organometallic Compounds

The advantages of chemical ionization outlined in Section 5.1, and the complementary nature of chemical ionization and electron-impact ionization naturally apply also to inorganic and organometallic substrates; however, little information is so far available on this topic[105, 106]. Borohydrides, as an example, have been investigated in some detail; in CI(CH_4) mass spectrometry they always yield intense $[MH]^+$ ions when terminal BH groups are present; in contrast $[M-H]^+$ fragments result from compounds containing terminal BH_2 groups[107]. Among the organometallic compounds there is apparently a more or less pronounced tendency to undergo redox reactions in accordance with eq. (l), depending on the nature of the metal, the ligand, and the reagent gas[108]. Such charge-exchange reactivity has been utilized to detect, for example, molecular ions from thermally very labile arsolanes[109].

[*] Aspects of quantitative analysis by means of mass spectrometry have recently been reviewed by *W. D. Lehmann* and *H.-R. Schulten*, Angew. Chem. *90*, 233 (1978); Angew. Chem. Int. Ed. Engl. *17*, 221 (1978).

[*] $[M]^{+\bullet}$ ions often occur with high intensity in CI(CH_4) spectra of aryl-substituted compounds or arenes (low values of ionization potential or recombination energy) as a result of charge-exchange processes.

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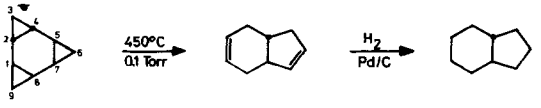
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Thermolysis of *endo,exo*-Tetracyclo[6.1.0.0^{2,4}.0^{5,7}]-nonane (*trans*-Tris-σ-homobenzene)[**]

By *Werner Spielmann, Dieter Kaufmann,* and *Armin de Meijere*[*]

Whereas all the hitherto known structural analogs of *cis*-tris-σ-homobenzene undergo [2+2+2] cycloreversions at 60 to 200°C to form derivatives[1] of *cis,cis,cis*-cyclonona-1,4,7-triene, the unsubstituted *trans*-tris-σ-homobenzene *(1)* is stable under these reaction conditions[2]. In contrast, its 3,3,6,6,9,9-hexamethyl derivative rearranges reversibly to hexamethyl-*trans*-tricyclo[4.3.0.0^{7,9}]non-3-ene above 120°C[3]. The ease of this reaction, suspected to involve a [$_\sigma 2_s + _\sigma 2_a$] process[3], could be attributable to the molecular geometry which is determined to some extent by the steric effect of the methyl groups[4].

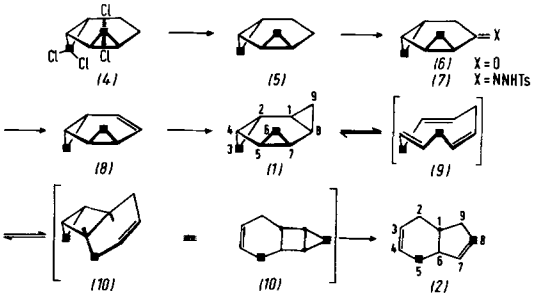
We have now found that the parent hydrocarbon *(1)* also undergoes a rearrangement at 380—400°C in a flow apparatus (contact time 10—75 s), which is *ca.* 75% uniform. The major product isolated by gas chromatography is shown by its ^{1}H- and ^{13}C-NMR spectra (Table 1) to be *trans*-bicyclo[4.3.0]nona-3,7-diene *(2)*. On catalytic hydrogenation (2 mol hydrogen) it affords *trans*-bicyclo[4.3.0]nonane *(3)*, the ^{1}H-NMR spectrum of which (Table 1) differs substantially from that of the *cis* isomer. The overall reaction of *(1)* obeys



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

first order kinetics; the activation parameters are $E_a = 175.7 \pm 3.8$ kJ mol^{-1}, $\log A = 13.39$ ($\Delta H^{\ddagger}_{298} = 173.2 \pm 3.8$ kJ mol^{-1}, $\Delta S^{\ddagger} = 3.14$ J mol^{-1} K^{-1})[5].

More detailed information about the mechanism of the major reactions comes from an examination of the [3,6-^{12}C$_2$]-labeled hydrocarbon *(1b)* prepared by a new method. Addition of dichlorocarbene (from $^{12}CHCl_3$) to 1,3-cyclohexadiene



led to *(4b)* (68% yield), which on reduction with $LiAlH_4$ in diglyme gave the hydrocarbon *(5b)* (73%). Compound *(5b)* was oxidized on silica gel with ozone to the ketone *(6b)* (44%)[6]; the tosylhydrazone *(7b)* (78%) of this ketone was treated with methyllithium in ether to give the olefin *(8b)* (78%), which could be cyclopropanated by the Simmons-Smith method to form *(1b)* (45%). Unlabeled *(1)* was obtained analogously.

Table 1. ^{1}H- and ^{13}C-NMR data.

^{1}H-NMR δ_{TMS} (signal shape, rel. int.)		
(1)	*(2)*	*(3)*
1.23–0.87 (m, 5H)	5.78 (s, 2H)	2.00–1.18 (bm, 9H)
0.79 (mc, 2H)	5.67 (m, 2H)	0.92 (bs, 7H)
0.51 (mc, 2H)	2.54–1.56 (bm, 8H)	
0.27 (mc, 1H)		
0.07 (mc, 2H)		

^{13}C-NMR δ_{TMS} (rel. int.)			
(1a)	*(1b)*	*(2a)*	*(2b)*
11.05 (2.1)	11.05 (1.6)	134.68 (1.0)	134.68 (1.0)
10.81 (1.0)	—	131.22 (1.2)	—
9.45 (2.0)	9.45 (1.0)	128.26 (1.2)	128.26 (1.3)
8.06 (2.0)	8.06 (1.6)	127.15 (1.1)	127.15 (1.4)
7.59 (1.7)	7.59 (1.9)	46.85 (1.1)	46.85 (0.9)
		44.49 (1.1)	44.49 (1.3)
		37.22 (1.2)	37.21 (1.6)
		31.11 (1.4)	31.11 (0.6)
		30.89 (1.2)	30.87 (0.6)

Thermolysis of *(1b)* gave a bicyclononadiene *(2b)*, the ^{13}C-NMR spectrum of which contained no signal for C-8 and the signals for C-2 and C-5 were only half as strong as in the spectrum of *(1a)*. If *(2b)* were formed by a [$_\sigma 2_s + _\sigma 2_a$] cycloaddition between the C-2/C-4 and C-5/C-7 bonds[7] of *(1b)* the ^{12}C label should appear in the ratio 50:75:75 at C-8, C-2, and C-5. The 100:50:50 distribution actually found rather indicates a mechanism in which primarily all three cyclopropane rings open—stepwise or synchronously as a [$_\sigma 2_s + _\sigma 2_s + _\sigma 2_s$] process—to give *cis,trans,trans*-1,4,7-cyclononatriene *(9)*. A [$_\pi 2_s + _\pi 2_a$] cycloaddition between the two strained *trans* double bonds[8] then leads to *(10)*, which rearranges to *(2)* with retention of the characteristic *trans* linkage.

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Only the final step of this sequence is irreversible; in the hexamethyl derivative of *(1)*, in which the $+I$ effect of the methyl group probably lowers the energy of the first, presumably rate-determining transition state, this last step does not occur and the reversibility of the first two becomes obvious from the equilibrium position of the overall reaction[3].

Thus it has been demonstrated that the thermal rearrangement, at least of unbridged[9] *trans*-tris-σ-homobenzenes, is also partly determined by the same [2+2+2] cycloreversion that is characteristic of the *cis* isomers[1]. The value of the activation energy found for *(1)* provides grounds for believing that *(10)* and maybe even *(9)*[10] could be isolable under flash-pyrolysis conditions.

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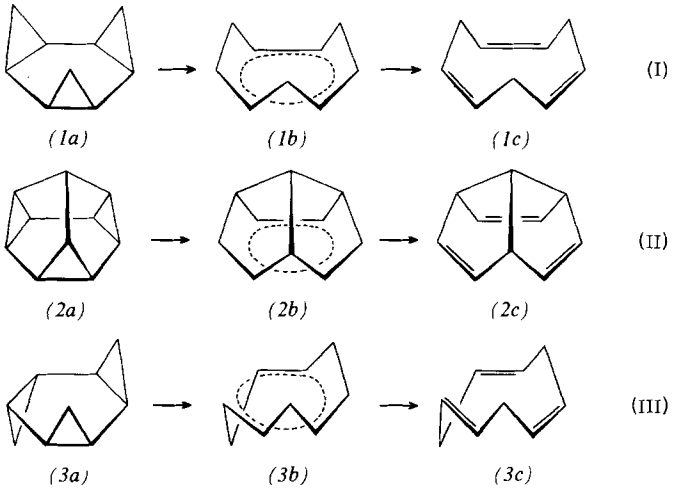
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Rearrangement of Tris-σ-homobenzenes to 1,4,7-Cyclononatrienes[**]

By *Jens Spanget-Larsen* and *Rolf Gleiter*[*]

Thermal isomerization of *cis*-tris-σ-homobenzenes to π isomers is regarded as a $[\sigma 2_s + \sigma 2_s + \sigma 2_s]$ cycloreversion[1, 2]; the geometry of the transition state is assumed to resemble that of the corresponding trishomobenzene ("trishomoaromatic"). With the aim of substantiating this classification, based on stereoelectronic, kinetic, and thermochemical criteria, and of characterizing such reactions in greater detail, we have calculated (MINDO/3[3]) part of the multidimensional potential energy surface for the carbocyclic cases (I—III).



In the case of (I) the calculation was performed with variation of all geometrical parameters without symmetry constraints (see Tables 1 and 2). It qualitatively reproduces the structural parameters expected for *(1a)*[4] and known for *(1c)*[5], the estimated H_f values (269.1 and 191.3 kJ mol^{-1}[1a]), and the activation energy ($E_a = 100$—126 kJ mol^{-1}[2, 6]) extrapolated from numerous model reactions. According to the correlation diagram (Fig. 1) the highly symmetrical transition state *(1b)*, which is consistent with a concerted reaction course, is already reached on elongation of the cyclopropane C—C bond to 1.9 Å.

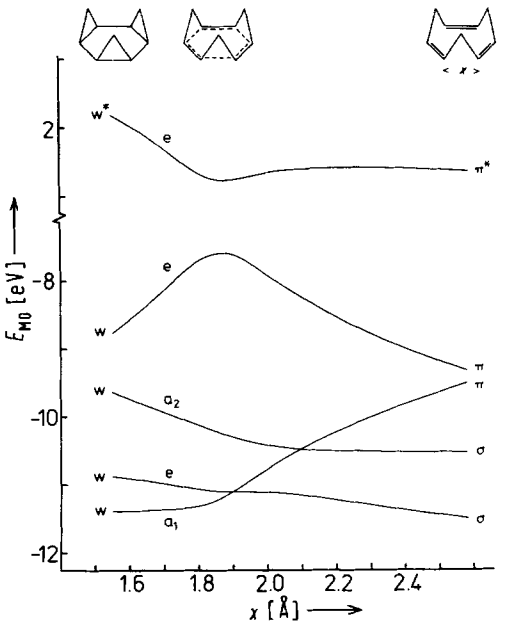
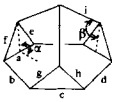


Fig. 1. Orbital energies *(1a)* as a function of the length x of the bonds broken during reaction (I). The symmetry is C_{3v} (w = Walsh orbital).

Table 1. Calculated bond lengths [Å] and bond angles according to MINDO/3. Values refer to C_{3v} symmetry for *(1a)*—*(1c)* and *(2a)*—*(2c)*, and to C_s symmetry for *(3a)*—*(3c)*; the symmetry plane passes through *a* and *d*.



(1a) $a = 1.552$, $b = 1.508$, $e = 1.505$, $ef = 62.1°$, $\alpha = 121.0°$
(1b) $a = 1.88$, $b = 1.408$, $e = 1.479$, $ef = 78.9°$, $\alpha = 124.5°$
(1c) $a = 2.573$, $b = 1.344$, $e = 1.494$, $ef = 119.5°$, $\alpha = 125.1°$

(2a) $a = 1.535$, $b = 1.525$, $e = 1.539$, $i = 1.565$, $ef = 59.8°$, $\alpha = 94.3°$, $\beta = 110.2°$
(2b) $a = 1.90$, $b = 1.413$, $e = 1.503$, $i = 1.581$, $ef = 78.4°$, $\alpha = 93.9°$, $\beta = 110.1°$
(2c) $a = 2.637$, $b = 1.349$, $e = 1.517$, $i = 1.578$, $ef = 120.7°$, $\alpha = 84.4°$, $\beta = 117.1°$

(3a) $a = 1.545$, $b = 1.510$, $c = 1.548$, $d = 1.511$, $e = 1.505$, $g = 1.504$, $h = 1.505$, $ab = 120.0°$, $bc = 120.0°$, $cd = 119.9°$, $\alpha = 241.9°$, $ef = 61.8°$, $gh = 61.9°$, $bg = 126.3°$, $dh = 129.7°$
(3b) $a = 1.82$, $b = 1.413$, $c = 1.92$, $d = 1.406$, $e = 1.484$, $g = 1.480$, $h = 1.478$, $ab = 119.5°$, $bc = 119.8°$, $cd = 118.1°$, $\alpha = 228.5°$, $ef = 75.6°$, $gh = 80.9°$, $bg = 126.9°$, $dh = 140.0°$
(3c) $a = 2.296$, $b = 1.349$, $c = 2.536$, $d = 1.351$, $e = 1.502$, $g = 1.488$, $h = 1.501$, $ab = 107.9°$, $bc = 122.2°$, $cd = 110.5°$, $\alpha = 211.5°$, $ef = 99.7°$, $gh = 116.1°$, $bg = 130.2°$, $dh = 141.1°$

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Table 2. Calculated heats of formation (H_f) and activation energies (E_a) according to MINDO/3.

	H_f [kJ/mol]	E_a [kJ/mol]	E_a^{el} [eV]	E_a^{core} [eV]
(1a)	221.0	151.9	70.18	− 68.60
(1b)	372.9	−263.3	229.70	−232.42
(1c)	109.6			
(2a)	445.3	223.0	70.05	− 67.75
(2b)	668.3	−338.5	231.33	−234.82
(2c)	329.8			
(3a)	211.8	202.5	72.48	− 70.39
(3b)	414.3	−180.8	159.66	−161.53
(3c)	233.5			

C_{3v} and C_s symmetry was assumed for the calculations on (II) and (III), respectively. The structural data calculated for *(2c)* and *(3c)* agree well with those obtained experimentally[7] or from force field calculations[8]. The slight difference of 22 kJ mol^{-1} in the H_f values of *(3a)* and *(3c)* is remarkable. This suggests that *(3a)* should be accompanied by a detectable amount of *(3c)* in equilibrium (III) at elevated temperatures[9]. The predicted activation energies are too high, but do reproduce the correct trend, *i.e.* that *(1a)* has a lower kinetic stability than *(2a)* and *(3a)*.

Interestingly, the electronic component of the activation energy E_a^{el} (Table 2) is higher for (I) than for (II). Only the energy term for core-core interaction is responsible for the lower activation energy of (I) (Table 2). The lower stability of *(1a)* compared with *(2a)* and *(3a)* can be partly explained by a decrease of the interaction between the CH_2 groups in the transition *(1a)*→*(1b)*. The shortest H···H distance between the CH_2 groups increases from 2.75 Å in *(1a)* to 2.91 Å in *(1b)*. No such decrease in nonbonded interactions is observed in (II) and (III).

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^{15}N-NMR Investigation of Solvent Effects on Sulfonamides[1]

By *Hans R. Kricheldorf*[*]

Two surprising effects have been observed in the ^{15}N-NMR spectra of poly(tauryl-ε-aminocaproyl)[1]: Firstly, the sulfonamide signal in caustic soda (pH = 13.5) appears about 13 ppm further downfield than in trifluoroacetic acid, while the carboxamide signal is shifted upfield; secondly, the signal intensity is reduced to *ca.* ¼ of its original value. We have now examined these solvent effects more closely on methanesulfonamide, which besides being readily soluble in many solvents has the added advantage that a onefold deprotonation at the NH_2 group influences the relaxation time T_1 and thus also the signal intensity only slightly. No ^{15}N-NMR signals can be observed at pH ≥ 10, but one is observed in the pH range 1.0—8.5. On addition of 3 mol % EDTA a signal also appears at pH ≥ 10 which has the same intensity as that at pH < 8.5. It therefore follows that the reduction in signal intensity in alkaline medium is mainly caused by paramagnetic cations. The traces of such ions in tap water do not suffice to influence the neutral sulfonamide group, but in the case of sulfonamide anions, which are better ligands they can lead to "signal nulling"[2].

The chemical shifts of methanesulfonamide in water at various pH values show the course of a titration curve with the anionic branch at low field. The turning point lies at pH = 10.4 to 10.6 and δ = −279 if the maximum value of the chemical shift in the alkaline range is taken to be −273.5 (cf. Table 1). The larger downfield shift in 8 N caustic soda can arise from the very high concentration of electrolyte. In organic solvents the direction of the chemical shift is analogous to the aqueous medium. Thus, the signals of various sulfonamides in dimethyl sulfoxide, which can function only as an acceptor for hydrogen bonds, are always found at lower field than in acidic, protonic solvents. Hence, in the case of sulfonamides the solvent effects are in direct contrast to a simple electron density shift correlation and also in contrast to the behavior of carboxamides, which exhibit downfield shifts of up to 30 ppm with increasing solvent acidity[3].

Table 1. ^{15}N-NMR shift δ (ppm upfield rel. $NO_3^{\ominus}$ ext.) of methanesulfonamide in various solvents.

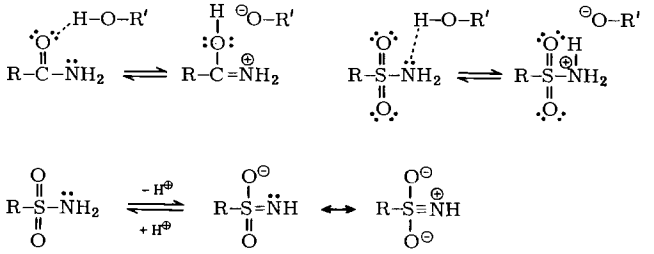
Water at pH	δ	Solvent	δ
1.0— 1.1	−284.4	Dimethyl sulfoxide	−281.3
4.0— 4.1	−284.4	Acetone	−285.6
6.4— 6.5	−284.6	Methanol	−287.1
8.5— 8.6	−284.5	Formic acid	−286.3
10.0—10.1	−283.2 [a]	Trifluoroacetic acid	−289.0
11.1—11.2	−273.5	Dimethyl sulfoxide [b]	−281.7
11.7—11.8	−273.6	Trifluoroacetic acid [b]	−289.3
12.3—12.4	−273.5	Dimethyl sulfoxide [c]	−293.2
8 N caustic soda	−271.8	Trifluoroacetic acid [c]	−297.3

[a] Broad signal; sharp signals in all other measurements. [b] *N-tert*-Butylmethanesulfonamide. [c] Methanesulfonanilide.

A qualitative interpretation of these findings must take into consideration that in the ^{15}N nucleus, as in the ^{13}C nucleus, the paramagnetic term of the shielding constant (σ_p) dominates. Though this means that the electron density has an influence on the chemical shift, other factors are also of importance, *e.g.* the degree of delocalization of n- and π-electrons, and thus their excitation energies, and the anisotropy of the electron density distribution. It is known from ^{1}N-NMR investigations[4] that carboxamides are attacked at the oxygen atom during hydrogen bond formation and protonation. The delocalization of the N-electrons is thereby enhanced, the anisotropy increased, and the absolute electron density decreased. In the case of sulfonamides, however, the hydrogen bridges attack at the nitrogen atom[3] and thus effect a delocalization of the electron pair, until in the limiting case of protonation an sp^3 hybridized N atom with largely isotropic electron density distribution is formed. In contrast to the carbonyl

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group, the sulfonyl group can delocalize two electron pairs; hence, deprotonation in the case of sulfonamides leads to increased anisotropy, as does protonation in the case of carboxamides. As in many other cases, the influence of the absolute electron density on the chemical shift would appear here also to be only of secondary importance[5].



Apart from their theoretical significance, the solvent effects can be of analytical utility in the case of amides, for they permit simple identification of sulfonamide signals besides the signals of carboxamides, urethanes and urea derivatives, which usually appear in the same spectral region.

Experimental

All ^{15}N-NMR spectra were recorded with an FT instrument (Bruker WH-90) at 21 kG (=9.12 MHz) [1 K data points to 200 Hz spectral width, pulse interval 2.54 s, pulse width 30 µs (*ca.* 30—40° depending upon the solvent), 3500—4000 pulses]. 2.8 g (≈30 mmol) of methanesulfonamide was dissolved in 10 ml of solvent and, in the case of alkaline solutions, 300 mg EDTA were added. The measurements were carried out in 20 mm sample tubes with a coaxial 5 mm capillary which contained D_2O as "lock". Isotope enriched NH_4NO_3 in D_2O (5 mm capillary) was used as reference standard. All amides of natural isotopic composition were measured.

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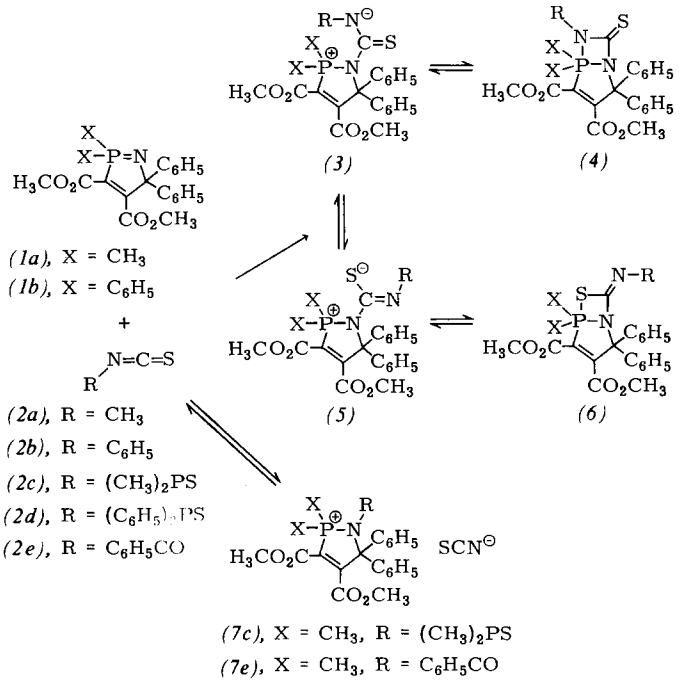
CAS Registry number:
Methanesulfonamide, 3144-09-0

[1] ^{15}N-NMR Spectroscopy.—Part 6.—Part 5: *H. R. Kricheldorf, W. E. Hull*, J. Macromol. Chem., in press.
[2] *G. E. Hawkes, W. M. Litchman, E. W. Randall*, J. Magn. Reson. *19*, 255 (1975); *C. S. Irving, A. Lapidot*, J. Am. Chem. Soc. *97*, 5954 (1975).
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[5] *M. Witanowski, G. A. Webb*: Nitrogen NMR. Plenum Press, London 1973.

Various Adducts of Isothiocyanates to the λ^5-Phosphazene Group of an Azaphosphole[1]

By *Alfred Schmidpeter* and *Thomas von Criegern*[*]

A phosphazene group incorporated into a five-membered ring as in the 1,2λ^5-azaphospholes *(1)* exhibits a considerably greater readiness to undergo cycloaddition than in the acyclic case[2]. Thus, on treatment with alkyl, aryl, and acyl isothiocyanates *(2)*, compounds *(1a)* and *(1b)* give stable [2+2] cycloadducts which can be isolated in crystalline form. Methyl isothiocyanate *(2a)* is found to add *via* the CN bond to give *(4)*, and the other isothiocyanates studied *(2b)*—*(2e)* *via* the CS bond to form *(6)*. The products are homogeneous as shown by their IR spectra. Compounds *(6)* contain the hitherto unknown 1,3,2λ^5-thiazaphosphetidine ring.



In solution, the situation shifts somewhat in favor of *(4)*. While the equilibrium still lies completely on the side of *(4)* for R=CH_3, and completely on the side of *(6)* for R=$(C_6H_5)_2PS$ and C_6H_5CO, there is considerable rearrangement of *(6)* to *(4)* when R=C_6H_5 and $(CH_3)_2PS$.

X	R		*(4)* : *(6)*
CH_3	C_6H_5	0.8 M $CDCl_3$	60 : 40
CH_3	$(CH_3)_2PS$	0.9 M C_6H_6	20 : 80
CH_3	$(CH_3)_2PS$	1.0 M $CDCl_3$	45 : 55
CH_3	$(CH_3)_2PS$	1.0 M $(CH_3)_2SO$	40 : 60

Ring closure and the resulting pentacoordination of the bridgehead phosphorus is established both for *(4)* and for *(6)* by the upfield shift of δ^{31}P (solution in $CDCl_3$) = −30 to −50 and −20 to −40, respectively. In benzene the shifts are generally at still higher field and in dimethyl sulfoxide at lower field. This dependence is particularly pronounced in adducts with electron-withdrawing groups R (δ^{31}P shift of about 20). It is interpreted as being due to slight participation of the zwitterionic forms *(3)* and *(5)*, which are favored by polar solvents. *(3)* and *(5)* are obviously separated from each other by a rotational barrier. Only at temperatures of 70 to 90 °C does the rearrangement *(3, 4)*/*(5, 6)* become fast enough for coalescence of the ^{1}H(PCH_3) signals of the two isomeric adducts. Rearrangement is intramolecular and does not proceed *via* reverse dissociation such as *(6)* ⇄ *(1)* + *(2)* ⇄ *(4)*. This follows from the failure of added azaphosphole *(1a)* to participate in coalescence.

A third isomeric adduct is observed on reaction of *(1a)* with *(2a)* and with *(2e)* in benzene: 1-dimethylthiophos-

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phinoyl- and 1-benzoyl-azaphospholium thiocyanate *(7c)* and *(7e)*, respectively. They are formed to the extent of about 2/3 as a result of kinetic control and are prevented from undergoing fast subsequent reaction by their sparing solubility in benzene. In chloroform solution *(7c)* is transformed, *via* regeneration of *(1a)* and *(2c)* (observable by NMR spectroscopy) into a solution of an equilibrium mixture of *(4)*, *(6)*; the same reaction also occurs somewhat slower in benzene suspension.

7-Methyl-5,7-diaza-1-phosphabicyclo[3.2.0]hept-2-ene-6-thiones (4) and 7-thia-5-aza-1-phosphabicyclo[3.2.0]hept-2-en-6-imines (6)

The yellow color of a concentrated solution of *(1)* in $CHCl_3$ or CH_2Cl_2 largely or completely disappears on addition of an excess of isothiocyanate *(2)*. The cycloadducts *(4)*, R = CH_3, or *(6)*, R = C_6H_5, $(CH_3)_2PS$, $(C_6H_5)_2PS$, C_6H_5CO, precipitate as colorless crystals, either spontaneously or on addition of *n*-pentane.

2,2-Dimethyl-1-dimethylthiophosphinoyl- and -1-benzoyl-1,2-azaphospholium thiocyanates (7)

On addition of an equimolar amount of the isothiocyanates *(2c)* or *(2e)* to a solution of *(1a)* (10 mmol) in benzene (250 ml), a voluminous colorless crystalline precipitate of *(7c)* or *(7e)* is immediately formed. Only *(7e)* can be recrystallized without decomposition from acetonitrile.

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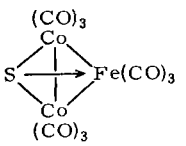
[1] Four- and Five-Membered Phosphorus Heterocycles, Part 30; also: Phosphazenes, Part 63. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Parts 29 and 62, respectively: [2c] and *A. Schmidpeter, J. Högel*, Chem. Ber., in press.

[2] a) *A. Schmidpeter, J. Luber*, Phosphorus 5, 55 (1974); b) *A. Schmidpeter, T. v. Criegern*, Angew. Chem. 90, 64 (1978); Angew. Chem. Int. Ed. Engl. 17, 55 (1978); c) J. Chem. Soc. Chem. Commun., in press.

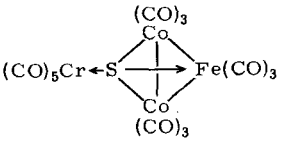
$(CO)_5Cr \cdot SFeCo_2(CO)_9$: An Organometallic Donor-Acceptor Complex[**]

By *Felix Richter* and *Heinrich Vahrenkamp*[*]

While the sulfur ions in the solid state structures of metal sulfides are usually surrounded by four or six metal ions, six-coordination of sulfur by metals is unknown in the covalent complexes, and four-coordination of the sulfur atoms is very rare[1]. This could be rationalized by assuming that in a covalent tetrahedral SM_4 arrangement two of the four metal-sulfur bonds must formally be donor-acceptor bonds, which would lead to accumulation of positive charge at the sulfur. Opposing evidence comes from the observation that complexes with SM_3 structural units release electrons very readily[2]; this is explainable in terms of accumulation of negative charge density as a result of linkage of the sulfur atom to three electropositive metal atoms. In the case of complex *(1)*[3] with a formal donor-acceptor (sulfur-metal) bond, the former argument would predict the absence of Lewis base properties whereas the latter argument would predict the complex to have good Lewis base properties.



(1)



(2)

Our experiment supports the latter alternative. *(1)* reacts with a solution of $(CO)_5Cr \cdot THF$ to give the new tetranuclear complex *(2)*. The composition of *(2)* is confirmed by elemental analysis and an EI mass spectrum. Its IR spectrum in the CO region (in cyclohexane: 2108 w, 2071 m, 2059 s, 2040 m, 2033 w, 1989 m, 1963 cm^{-1} s) can be reconstructed by combination of the spectrum of *(1)*[3] and the two typical bands of a $(CO)_5CrL$ complex. The structure suggested was confirmed by X-ray methods[4] (cf. Fig. 1). *(2)* is the first complex we know to have a sulfur atom linked to three different metal atoms.

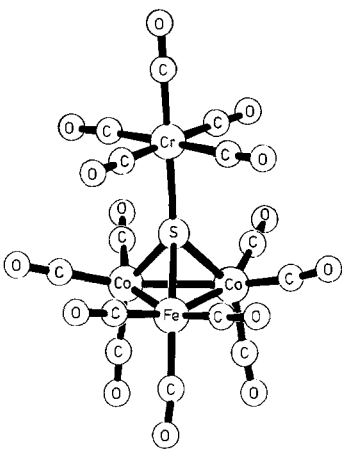


Fig. 1. Molecular structure of the tetranuclear complex *(2)*. Bond lengths: Co—Co and Fe—Co = 255.7 ± 0.3 pm, Co—S and Fe—S = 214.5 ± 0.5 pm, Cr—S = 235.1 pm. The Fe and Co atoms were assigned arbitrarily.

As in the structure of *(1)*[5a], the iron and cobalt atoms of *(2)* are indistinguishable by crystallography. Moreover, the donor complex *(1)* is almost unchanged in *(2)*: the metal-metal bond lengths are equal, and the metal sulfur bonds are shortened by only 1 pm. On the other hand, the Cr—S bond in *(2)* is significantly shorter than in other $(CO)_5CrL$ complexes containing sulfur ligands[6]. Both results can be interpreted by assuming the S→Cr σ donor function to induce a comparably strong S←Cr π acceptor function, which strengthens the Cr—S bond and balances the electronic requirements of the "ligand" *(1)*.

The organometallic Lewis base *(1)* is much less reactive than the isoelectronic compound $PCo_3(CO)_9$[7], which even reacts with itself at room temperature. The reason is probably that the HOMO in *(1)* does not correspond to the sulfur lone pair[5b]. This fact and the bond delocalization apparent from the structure and the IR spectrum of *(2)* justify the conclusion that the cluster *(1)* is an electron reservoir with properties similar to $RCCo_3(CO)_9$[8].

Procedure

A solution of *(1)* (280 mg, 0.6 mmol) in *n*-hexane (25 ml) is added to a solution of $(CO)_5Cr$ (0.6 mmol) in tetrahydrofuran (8 ml) generated by irradiation. The mixture is immediately

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cooled to −20°C and then, more slowly, to −40°C, whereupon black compound *(2)* precipitates [190 mg (46%); m.p. 107—109°C (dec.)]; the donor-acceptor complex is air-stable in the solid state but unstable in solution at room temperature.

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CAS Registry numbers:
(1), 22364-22-3; *(2)*, 66523-73-7; $Cr(CO)_5$, 26319-33-5

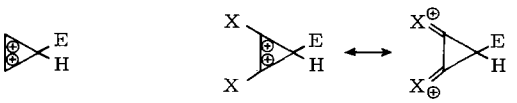
[1] *H. Vahrenkamp*, Angew. Chem. *87*, 363 (1975); Angew. Chem. Int. Ed. Engl. *14*, 322 (1975).
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[5] a) *D. L. Stevenson, C. H. Wei, L. F. Dahl*, J. Am. Chem. Soc. *93*, 6027 (1971); b) *C. E. Strouse, L. F. Dahl, ibid. 93*, 6032 (1971).
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S_E Reactions on the C_3^+-Ring: π-Attack[**]

By *Robert Weiss* and *Claus Priesner*[*]

All substitutions on the aromatic cyclopropenylium ion discovered so far are either variants of classical nucleophilic aromatic substitution[1] or 4z exchange reactions[2]. We now report the first example of an electrophilic aromatic substitution in this system.

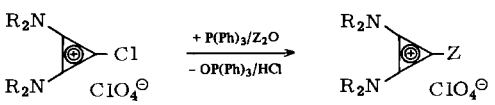
The hypothetical σ complex *(1)* possesses the unusual structure of an α,β-dicarbenium ion[3], suggesting *a priori* that electrophilic substitution at the C_3^+ ring requires the assistance of two strong donor groups according to *(2)*.



(1) *(2)*

E^+ = Electrophile, X = Donor substituent

If the readily accessible[1] cyclopropenylium salt *(3)* is subjected to redox hydrolysis with $P(Ph)_3/H_2O$ or $P(Ph)_3/D_2O$, then the substitution product *(4a)* or *(4b)* can be isolated in practically quantitative yield under mild conditions (CH_2Cl_2, *ca.* 20°C).



(3) *(4a)*, Z = H; *(4b)*, Z = D

R = *i*-C_3H_7

Compound *(4a)* has apparently already been obtained *via* another route by *Yoshida et al.* and has been repeatedly mentioned[4], but without citation of characteristic data. Compound *(4b)* was formerly unknown.

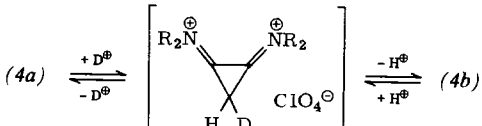
Table 1. Characteristic data of bis(diisopropylamino)cyclopropenylium perchlorate *(4a)* and its 3-deuterio derivative *(4b)*. Only end absorption is observed in the UV spectrum (CH_2Cl_2).

	M.p. [°C]	IR (KBr) [cm^{-1}]	^{1}H-NMR [a] τ	^{13}C-NMR [a] δ
(4a)	201—203 (dec.)	3105 (m) 2950 (m) 1895 (m) 1880 (m) 1570 (s)	2.6 (s, 1H) 6.1 (mc, 4H) 8.53/8.63 (d, $J=10$ Hz)	C-1,2 133.7 C-3 99.0
(4b)	203—205 (dec.)	2950 (m) 2350 (m) 1895 (m) 1880 (m) 1570 (s)	6.1 (mc, 4H) 8.53/8.63 (d, $J=10$ Hz)	

[a] In $CDCl_3$, rel. to TMS as internal standard.

The incomparably large upfield shift of the single ring proton in the ^{1}H-NMR spectrum of *(4a)* (cf. Table 1) shows that C-3 cannot be far removed from electroneutrality. The ^{13}C resonance frequency of this ring atom ($\delta=99.0$) even suggests a negative charge of −0.15 units[5]. Electrophilic attack at this ring site therefore appears feasible, even though the energy content of the corresponding σ-complex must be regarded as the decisive parameter. The transformation of *(4a)* into *(4b)* in acidic solution represents a model for such a reaction. No H/D exchange could be observed on the action of D_2O, CF_3CO_2D, or 50% D_2SO_4 on *(4a)*. However, the pure deuteration product *(4b)* could be isolated within a few minutes by dilution of a solution of *(4a)* in conc. D_2SO_4 with D_2O and extraction with CH_2Cl_2[6]. The reverse process *(4b)* → *(4a)* could also be accomplished in a corresponding manner and could also be detected in the mass spectrum of *(4b)*[2b, 10b].

The observed reaction conditions for this H/D exchange rule out a dissociation-recombination mechanism *via* a cyclopropenylidene intermediate[7] and are compatible only with electrophilic attack on the cyclopropenylium π-system according to the following scheme[8]:



(5)

Direct spectroscopic detection of a σ-complex *(5)* has not yet been possible; the steady state concentration of such a species, derived from the still unknown cyclopropanedione, should therefore be very low under our reaction conditions.

Both the π-electron distribution deduced from the NMR data of *(4a)* and the reaction behavior discussed above are in accord with a pronounced vinamidinium character[9] of this cyclopropenylium system. Although expected in principle[10a], the extent to which the 2π-aromatic C_3^+-ring loses its integrity under the perturbing influence of two strong donor groups is nevertheless surprising. Preliminary studies have shown[2b, 10b] that other electrophiles can also substitute the H atom attached to the ring of *(4a)*. Since the development of more effective alternative methods such reactions are of limited practical significance.

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[**] Functional *cyclo* C_3-Derivatives, Part 4. This work was supported by the Deutsche Forschungsgemeinschaft.—Ref. [2a] is to be regarded as Part 3.

CAS Registry numbers:
(3), 32269-08-2; *(4a)*, 57358-59-5; *(4b)*, 66633-42-9

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[2] a) *R. Weiss, C. Schlierf, K. Schloter*, J. Am. Chem. Soc. *98*, 4668 (1976); b) *R. Weiss*, Habilitationsschrift, Universität München 1976.
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[6] No anion exchange was observed.
[7] *R. Weiss, C. Priesner, H. Wolf*, Angew. Chem. *90*, 486 (1978); Angew. Chem. Int. Ed. Engl. *17*, 446 (1978).
[8] For the sake of simplicity, the σ complexes dideuterated and diprotonated at C-3 were not included in the scheme.
[9] Cf. *D. Lloyd, H. McNab*, Angew. Chem. *88*, 496 (1976); Angew. Chem. Int. Ed. Engl. *15*, 459 (1976). These authors raise the question whether diaminocyclopropenylium salts are to be regarded as special vinamidinium systems.
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S_E Reactions on the C_3^+-Ring: σ-Attack[**]

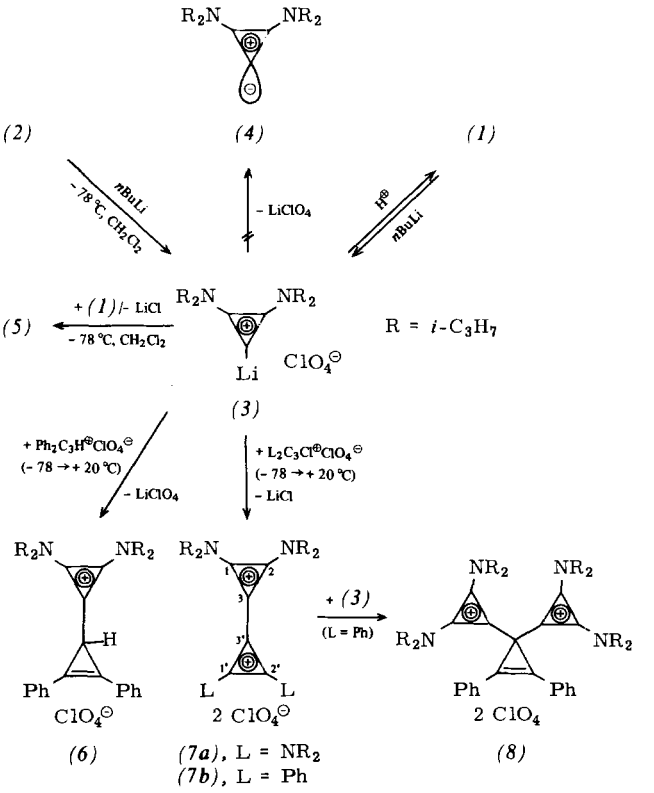
By *Robert Weiss, Claus Priesner*, and *Hilmar Wolf*[*]

We have demonstrated[1] for the cyclopropenylium salt *(1)* that the C_3^+-ring can in principle undergo electrophilic aromatic substitution.



(1) R = *i*-C_3H_7 *(2)*

However, such S_E reactions with the optimally stabilized π-system of *(1)* require relatively drastic conditions and are limited to the strongest electrophiles. In connection with studies on "coupled three-membered rings"[2], we wished to use cyclopropenylium derivatives as electrophilic components. These relatively weak electrophiles do not react with *(1)*. Replacement of the H atom attached to the ring of *(1)* by a more electrofugic group should facilitate S_E reactions on the activated σ-skeleton of the aromatic system. We now report the first halogen/lithium exchange on the C_3^+ ring of *(2)* and syntheses with the metallocyclopropenylium system *(3)* obtainable in this way [Scheme 1].



Scheme 1.

Addition of equimolar amounts of *n*-butyllithium in *n*-hexane to the readily accessible[3a] chlorine compound *(2)* in anhydrous dichloromethane[3b] at −78 °C gives a yellow solution from which the dehalogenation product *(1)*[1] can be isolated quantitatively by addition of water and subsequent thawing. This reaction demonstrates that quantitative halogen/metal exchange[4b] is possible for *(2)* as it is for haloacetylenes[4a]. The lithium derivative *(3)* is a possible reactive intermediate[5]; its generation is favored by two factors: on the one hand, the bond between the three-membered ring and the halogen is susceptible to S_N attack[4a] at the halogen owing to sp hybridization, and on the other the alternative nucleophilic attack at position 3 of the C_3^+-ring is greatly hindered owing to the cyanine character of *(2)*[1]. CH_2Cl_2 solutions of the resulting organometallic species remain homogeneous down to −40 °C, *i.e.* under the reaction conditions employed, no "free" cyclopropenylidene *(4)* is present, which is reported by *Yoshida* to arise from *(1)* and *n*BuLi[6a], since its formation would be accompanied by precipitation of a molar equivalent of $LiClO_4$ which is insoluble in CH_2Cl_2. Deposition of lithium salts is, however, observed in a series of S_E reactions with *(3)* (cf. Scheme 1). Thus reaction of *(3)* with the weak electrophile *(1)* at −78 °C is accompanied by precipitation of $LiClO_4$. The salt-like reaction product *(5)* isolated pure in 65 % yield is shown by analytical data to formally correspond to a 1:1 adduct of *(1)* and *(4)*, whose structure could not be completely elucidated. Spectroscopic data confirm that *(5)* contains an intact cyclopropenylium system [m.p. 151 °C (dec.); IR (KBr): 1905 (m), 1630 (s), 1535 (vs), 1465 (m), 1370 (m) cm^{-1}].

Remarkably, *(5)* is formed as the sole product (65 % yield) even when a CH_2Cl_2 solution of *(3)* is warmed from −78 °C to room temperature. The reaction does not start until the temperature has risen above −40 °C; precipitation of lithium salt and a brown coloration are observed. Compound *(3)* and the solvent probably afford *(1)* and $LiCHCl_2$ *via* a metala-

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tion equilibrium; recombination of *(3)* and *(1)* then yields the adduct *(5)*.

Reaction of *(3)* with the considerably more electrophilic 1,2-diphenylcyclopropenylium perchlorate instead of *(1)* gives the cyclopropenylcyclopropenylium salt *(6)* (cf. Scheme 1) whose spectroscopic data reveal the structural features of the two three-membered ring subunits [m.p. 181 °C (dec.); IR (KBr): 1900 (w), 1835 (m), 1535 (vs), 1440 (w), 1375 (w) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 1.28$ (mc, 24H), 3.33 (s, 1H), 3.85 (mc, 4H), 7.72 (mc, 10H); ^{13}C-NMR ($CDCl_3$): $\delta = 131.5$ (C-1,2), 113.5 (C-3), 109 (C-1',2'), 15.7 (C-3')].

As high-energy derivatives of the hardly investigated $C_6H_5^+$ series, compounds of type *(6)* warrant synthetic and theoretical interest[7]. The only stable representative obtained so far is the perphenylated analog[8]. The procedure presented in this communication provides a flexible[9] entry to high-energy isomers of phenyl cations[7b] so that corresponding series of rearrangements[7a] can now be studied on a broad basis.

In the same way, *(3)* and *(2)* give an 85% yield of the triafulvalene dication salt *(7a)* which was recently synthesized by *Yoshida et al.*[6b] from *(1)*, *(2)*, and *n*-BuLi. Our procedure is superior with regard to yields and convenience, and in particular disposes of the need for *(1)* as a precursor of *(3)*[10]. In the interests of further simplification, *(2)* can be subjected to a Wurtz reaction with only 0.5 equivalent of *n*-BuLi (cf. *Experimental*). Moreover, *(7a)* is also accessible by oxidative coupling of *(3)*, *e.g.*

$$2\,(3) \xrightarrow[CH_2Cl_2,\ -78\text{ to }20\,^\circ C]{+I_2/-LiI} (7a)$$

(7a) belongs to the $C_6H_4^{2+}$ series, which may provide a new entry to the $C_6H_5^+$ and C_6H_6 series with their great potential for rearrangement[2, 7a].

An attempt to synthesize the unsymmetrical dication system *(7b)* gave 3,3-dicyclopropenyliocyclopropene *(8)* in 60% yield as the sole product [m.p. 151 °C (dec.); IR (KBr): 1890 (w), 1805 (m), 1550 (vs), 1450 (w), 1380 (w) cm^{-1}; ^{1}H-NMR: $\delta = 7.67$ (mc, 10H), 4.0 (mc, 4H), 3.43 (mc, 4H), 1.40/1.50 (d, 24H, $J = 10$ Hz), 1.14/1.24 (d, 24H, $J = 10$ Hz); UV (CH_2Cl_2): $\lambda_{max} = 330$ nm ($\varepsilon = 16600$)]. The spectroscopic data show that the second attack of *(3)* on *(7b)* occurs regiospecifically at position 3'. The UV spectrum of *(8)* is especially characteristic of a 1,2-diphenylcyclopropene derivative[8].

The first representative of the 3,3-dicyclopropenyliocyclopropenes raises interesting questions regarding electronic interaction between the cyclic subunits.

Experimental

n-BuLi (1 mmol; *ca.* 0.7 ml of a 20% solution in *n*-hexane) is added dropwise at −78 °C to a solution of *(2)* (740 mg, 1 mmol) in anhydrous CH_2Cl_2 (20 ml). The mixture is allowed to warm slowly to room temperature, LiCl is filtered off, and the product precipitated with Et_2O. The analytically pure product still contains CH_2Cl_2 (1:1 adduct) which can be removed at 80 °C *in vacuo*. Yield: 590 mg (88%) of *(7a)*, m.p. 295 °C (dec.). The substance is identical with an authentic sample[6b].

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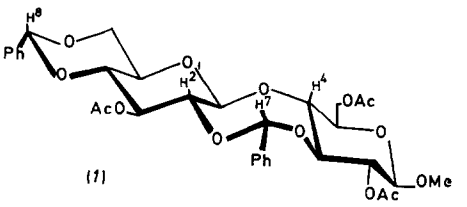
CAS Registry numbers:
(1), 57358-59-5; *(2)*, 32269-08-2; *(3)*, 66466-67-9; *(6)*, 66633-44-1; *(7a)*, 61695-57-6; *(7b)*, 66633-46-3; *(8)*, 66674-83-7; 1,2-diphenylcyclopropenylium perchlorate, 37647-36-2

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[10] Compound *(1)*, prepared from *(2)*, can also be transformed into *(3)* under the same conditions as *(2)*.

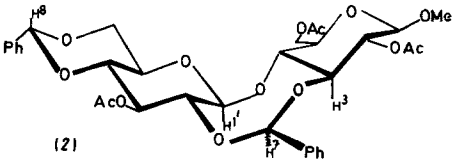
Structural Elucidation of Diastereoisomeric 1,3,6-Trioxacyclooctane Systems by Simultaneous Relaxation and Double Resonance Experiments[**]

By *Klaus Bock, Bernd Meyer*, and *Joachim Thiem*[*]

Reaction of methyl-β-D-cellobioside with benzylidene halide in pyridine[1] leads to a mixture of four methyl benzylidene-β-D-cellobiosides[2] which, after acetylation, can be resolved by various methods of separation into methyl penta-*O*-acetyl 4',6'-*O*-benzylidene-β-D-cellobioside (34%) and three isomeric methyl tri-*O*-acetyl-di-*O*-benzylidene-β-D-cellobiosides *(1)*—*(3)*[3]. Attempts to elucidate the structures of *(1)* and *(2)* by conventional NMR spectroscopic techniques have so far met without success. Interpretation of the NMR spectra in $CDCl_3$ and in C_6D_6 and normal double resonance investigations enabled assignment of only a limited number of structural units and location of a 4',6'-benzylidene moiety.



(1)



(2)

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Table 1. ^{1}H-NMR data [δ values] and T_1 values [s] for compounds *(1)* and *(2)*.

Cpd.	1-H	2-H	3-H	4-H	5-H	6a-H/6b-H	1'-H	2'-H	3'-H	4'-H	5'-H	6a'-H	6e'-H	7-H	8-H
(1) [a]	4.13 d	4.83 dd	3.60 m	3.73 t	3.49 ddd	4.3 m	4.85 d	4.27 dd	5.41 t	3.60 m	3.60 m	3.96 dd	4.3 m	5.94 s	5.50 s
(1) [b]	3.73 d	5.36 dd	3.67 dd	3.86 dd	3.2 m	4.45 m	4.56 d	4.16 dd	5.64 t	3.35 t	3.2 m	3.41 t	4.11 dd	6.09 s	5.35 s
(1) [c]	0.53	1.18	0.38	0.41	—	—	0.57	0.42	0.88	—	—	—	—	0.68	0.58
(1) [d]	0.61	1.35	0.44	0.43	—	0.32	0.60 [e]	0.55 [e]	0.97	—	—	0.31	0.30	0.78	0.65
(2) [f]	4.42 d	5.14 dd	3.74 dd	4.04 t	3.7 m	4.4 m	4.82 d	4.23 t	5.33 t	3.5 m		3.66 m	4.36 m	5.91 s	5.45 s
(2) [g]	4.16 d	5.52 dd	3.35 dd	3.83 t	3.4 m	4.45 m	4.47 d	4.05 dd	5.54 t	3.22 t	3.04 ddd	3.34 t	4.07 dd	5.86 s	5.32 s
(2) [h]	0.53	1.13	0.72 [e]	0.44	0.42	—	0.58 [e]	0.34	0.81	—	—	—	—	0.93	0.59
(2) [i]	0.56	1.34	0.66	0.44	—	—	0.56	0.41	0.85	0.41	—	—	—	0.90	0.60

[a] $c = 0.0506$ M in $CDCl_3$; OCH_3 3.40 s, OAc 1.87 s, 2.03 s, 2.09 s, aryl 7.41 mc. [b] $c = 0.03$ M in C_6D_6; OCH_3 3.16 s, OAc 1.61 s, 1.70 s, 1.71 s, aryl 7.85 m, 7.14 m. [c] $c = 0.030$ M in $CDCl_3$, $T = 294$ K. [d] $c = 0.0302$ M in C_6D_6, $T = 297$ K. [e] Data obtained from zero crossover point. [f] $c = 0.0425$ M in $CDCl_3$; OCH_3 3.52 s, OAc 1.60 s, 1.91 s, 2.12 s, aryl 7.36 mc. [g] $c = 0.0302$ M in C_6D_6; OCH_3 3.26 s, OAc 1.38 s, 1.62 s, 1.72 s, aryl 7.56 m, 7.12 m. [h] $c = 0.0305$ M in $CDCl_3$, $T = 294$ K. [i] $c = 0.0305$ M in C_6D_5, $T = 297$ K.

On measurement of the T_1 values by the inversion recovery method[4] some of the signals in the complex multiplets show sufficiently different spin-lattice relaxation times (see Table 1) that individual signals can readily be observed at zero crossover point of the other signals. However, since both carbohydrate rings have a β-D-*gluco* configuration with only axial ring protons, assignment of the signals from the coupling constants alone was impossible. We therefore decided to carry out simultaneous inversion recovery and double resonance measurements on the products. In this way it was possible to assign couplings to protons normally superposed by multiplets.

The spectra obtained for one experiment on using this approach in the case of *(1)* are shown in Figure 1. At a delay of 0.33 s between 180° and 90° pulses all the proton signals of the multiplet at δ = 3.60 (4'-H, 5'-H, 3-H), apart from that for 3-H, display zero intensity (see Fig. 1b), thus leaving the 3-H signal unsuperposed and clearly discernable. Irradiation of 2-H during the inversion recovery measurement (Fig. 1c) allows undisturbed observation of the effect at 3-H. Using this new technique we have been able to completely assign the NMR spectra of compounds *(1)* and *(2)*.

The results show that both *(1)* and *(2)* have an unusual structure in which the second benzylidene ring additionally binds the two β,1→4-glycosidically linked glucose rings *via* the atoms C-3 and C-2', while the remaining three acetoxy groups are sited on C-2, C-6, and C-3'. We are therefore dealing with a 1,3,6-trioxacyclooctane system. While the absolute configuration of all ring atoms in the saccharide is known, an assignment for the chiral acetal C-atom in the eight-membered ring (C-7) is still lacking.

On measurement of the nuclear Overhauser effect (NOE), irradiation of 7-H of *(1)* leads to distinct enhancement in intensity of only the 2'-H signal. When the same experiment is carried out on *(2)* the signal intensity of 3-H is enhanced. Saturation of 3-H in *(2)* expectedly gives a distinct nuclear

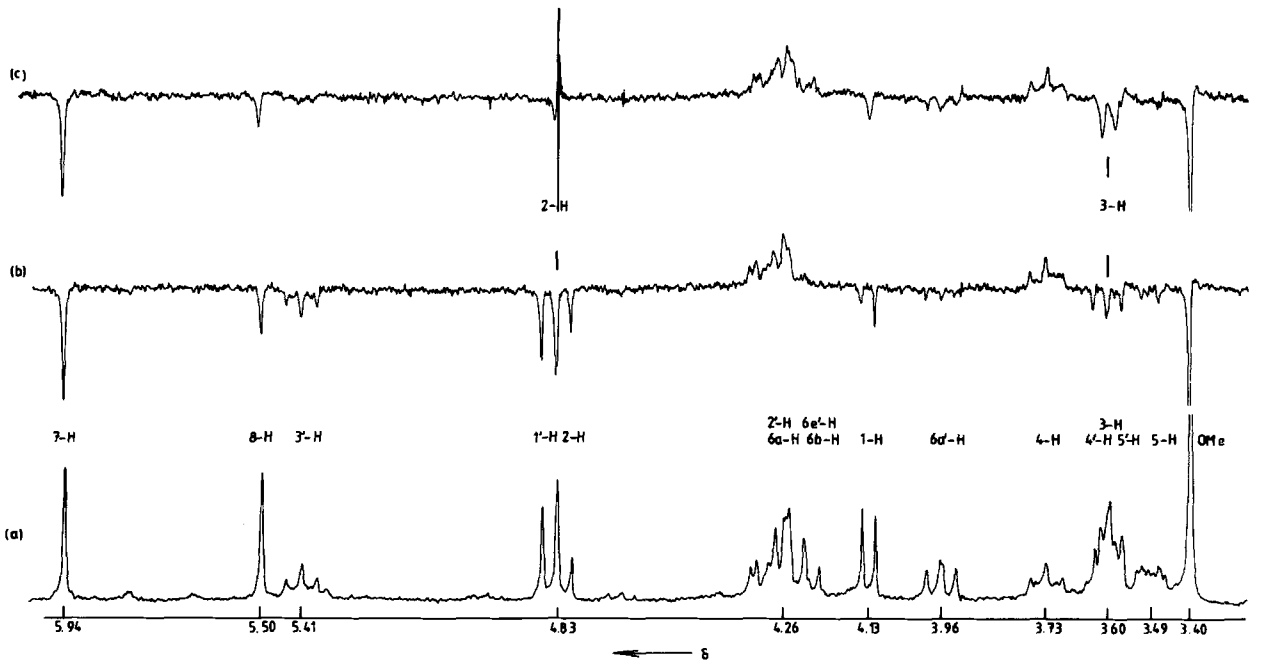


Fig. 1. a) Section from the 270-MHz ^{1}H-NMR spectrum of *(1)* in $CDCl_3$ ($c = 0.03$ mol/l, $T = 294$ K) from δ = 3.40—5.94; b) inversion recovery ($\tau_1 = 0.33$ s); c) inversion recovery as in (b) in combination with double resonance experiment at the frequency of 2-H.

Table 2. ^{1}H-NMR coupling constants J [Hz] of compounds *(1)* and *(2)*.

Cpd.	1,2	2,3	3,4	4,5	5,6a	5,6b	6a,6b	1',2'	2',3'	3',4'	4',5'	5',6a'	5',6e'	6a',6e'
(1)	8.2	9.2	7.8	9.8	4.2	2.6	—	8.8	9.8	9.4	9.4	10.3	4.8	10.3
(2)	8.0	9.9	8.8	9.5	—	—	—	8.8	9.5	9.5	9.5	10.4	5.2	10.4

Overhauser effect at 7-H and a still noticeable effect at 1'-H. Hence compound *(1)* has C-7-(*S*) chirality, while *(2)* is the (*R*)-diastereomer.

As can be deduced from the coupling constants (Table 2) the non-reducing glucose ring in *(1)* and *(2)*, which together with the condensed 1,3-dioxane ring forms a *trans*-trioxadecalin system, is present in a $^4C_1$ chair conformation. Only the $J_{1'2'}$ coupling constant (8.8 Hz) is greater than in normal disaccharides, presumably as a result of the condensed eight-membered ring. The reducing glucose ring also shows a definite $^4C_1$ chair conformation; but only in the case of *(1)* is a noticeably reduced transdiaxial coupling constant ($J_{3,4}$ = 7.8 Hz) observed.

According to studies with Dreiding models the 1,3,6-trioxacyclooctane structural unit in both *(1)* and *(2)* can be present in rigid twisted conformations or flexible "tub-chair" conformations, while butterfly ("tub-tub") or crown ("chair-chair") conformations[5] can be ruled out. Determination of the relative positions of the β,1→4-linked saccharides revealed the torsion angles 1'-H, C-1', C-4, O-4 (θ_1) and C-1', O-4, C-4, 4-H (θ_2) of $\theta_1 = 120°$ and $\theta_2 = 30°$[6]. Measurements on a model of the "tub-chair" conformation gave for *(1)* $\theta_1 \approx 0°$ and $\theta_2 \approx 150$—$180°$, consistent with an highly stretched molecule. In the case of *(2)* the corresponding torsional angles are $\theta_1 \approx 150$—$180°$ and $\theta_2 \approx 0°$, resulting in a sickle-shaped molecule, as confirmed by X-ray structure analysis[7].

Thus, in each case the eight-membered ring system of the isomers *(1)* and *(2)* assumes a "chair-tub" or a "tub-chair" conformation, determined by the fixed chair conformations of the saccharide molecules.

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The First Oxostannate(II): $K_2Sn_2O_3$[1]

By *Rolf Michael Braun* and *Rudolf Hoppe*[*]

The amphoteric nature of $Sn(OH)_2$ has long been known. And yet no hydroxo- or oxostannate(II) of defined structure has so far been detected. At the end of a 25-year search we have now obtained the first single crystals of $K_2Sn_2O_3$ [1.1 $KO_{0.48}$ + SnO; under argon, sealed alumina cylinder, 550°C, 24 h (powder) or 7 d (single crystals)].

As a powder $K_2Sn_2O_3$ is deep yellow, while the platelet-shaped single crystals of hexagonal habit are brownish yellow. Hydrolysis takes place immediately on exposure to air, yielding black SnO. Dilute mineral acids readily dissolve the sample, leaving no residue.

$K_2Sn_2O_3$ forms trigonal-rhombohedral crystals, space group $R\bar{3}—C_{3i}^4$, with $a = 6.00_1$, $c = 14.33$ Å, $c/a = 2.39$, $Z = 3$. If c/a were $\sqrt{6} \approx 2.45$ the unit cell would show pseudo-cubic geometry, corresponding to the $K_2Pb_2O_3$ type[2]. $R = 4.7_2$ % [four-circle diffractometer data, Philips PW 1100, 348 *hkl*, $4° \leq \theta \leq 32°$; Mo-Kα; K^+ and Sn^{2+} refined anisotropically, not corrected for absorption (cf. Table 1)].

Table 1. Positional parameters [$\times 10^4$] and anisotropic temperature factors [$Å^2 \times 10^4$] of $K_2Sn_2O_3$ (standard deviations in parentheses).

Atom	x	y	z	$U_{11} = U_{22} = 2U_{12}$	U_{33}	$U_{23} = U_{13}$
K^1	0	0	7445(20)	183(10)	160(50)	0
K^2	0	0	2380(20)	220(10)	120(20)	0
Sn^1	0	0	0	106(5)	135(20)	0
Sn^2	0	0	4802(1)	79(4)	80(20)	0
O	1685(20)	3380(20)	618(10)	380(2)		

The anisotropic temperature factor has the form: $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^*c^* + 2U_{13}hla^*c^* + 2U_{12}hka^*b^*)]$

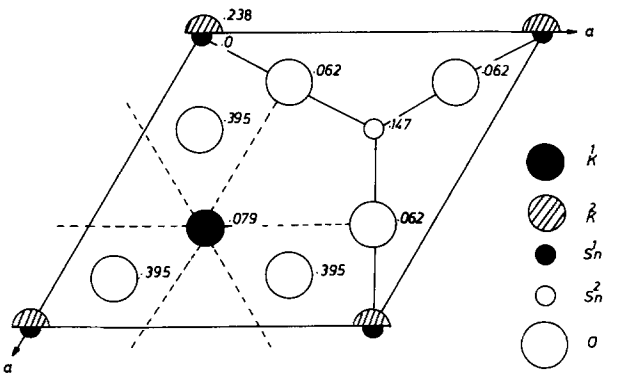


Fig. 1. Partial projection of crystal structure of $K_2Sn_2O_3$ along [001]; heights given in units of *c*.

Commensurate with $KSnO_{3/2}$, we are dealing with a perovskite variant in which half of the anions are missing in a regular manner. Unlike $KPbO_{3/2}$, however, in which the spatial network of the $PbO_{3/2}$ skeleton is retained, the present compound unexpectedly has a layer structure in which $Sn^{2+}—O_3^{2-}—Sn^{2+}$ layers are stacked parallel to the base in a rhombohedral sequence (cf. Fig. 1). Thus K^+ is partly in a distorted octahedral environment ($K^2—O$: 2.82_5 (3×), 3.07_7 (3×) Å) and partly in a hexagonal planar environment ($K^1—O$: 3.00_6 (3×), 3.01_2 (3×) Å). The Sn—O distances are 1.96_6 (Sn^1) (3×) and 2.09_9 (Sn^2) (3×) Å. The lone pair electrons of Sn^1 and Sn^2 are directed towards K^1 which thereby acquires the coordination number 8 (hexagonal bipyramid).

The *primary structure* is thus determined by the presence of two kinds of SnO_3 groups of symmetry C_{3v}, and the *secondary structure* by the fact that these groups are linked to form $Sn^1O_3Sn^2$ double layers; stacking of these layers along [001] is responsible for the *tertiary structure*. K^2 and K^1, which join the layers respectively *via* O^{2-} and *via* the Sn^{2+} lone pair electrons, are arranged between the layers.

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[1] Part of Doctoral Dissertation by *R. M. Braun*, Universität Giessen; Part of plenary lecture: *R. Hoppe:* Advances in preparative chemistry of oxides and fluorides, Solid State Chem. Eur. Meet., Strasbourg 1978.

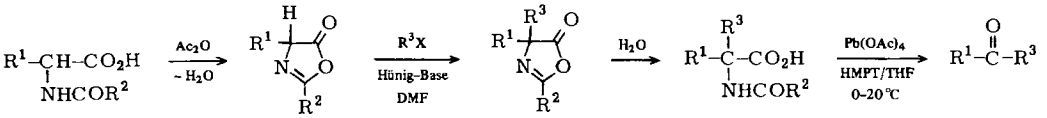
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α-Amino Acids as Nucleophilic Acyl Equivalents: Synthesis of Ketones and Aldehydes by Means of Oxazolin-5-ones[**]

By *Rainald Lohmar* and *Wolfgang Steglich*[*]

Oxidative degradation of α-amino acids to aldehydes, CO_2, and ammonia and its reversal, the Strecker amino acid synthesis, demonstrate that the C-2 atom of the amino acids is a carbonyl equivalent. *Stork et al.*[1] exploited this relationship for the synthesis of aldehydes and ketones by alkylation of *N*-benzylideneglycine ethyl ester. The substitution products were subsequently hydrolyzed, reduced with $LiAlH_4$, and cleaved with periodate.

We found that the 2-oxazolin-5-ones *(2)*, which are readily accessible from α-amino acids or their *N*-acyl derivatives *(1)*, are particularly suitable as nucleophilic acyl equivalents. They can be substituted in position 4 by reaction with alkyl, benzyl, and allyl halides, as well as other electrophilic reagents, to give 2-oxazolin-5-ones *(3)*[2] which after hydrolysis to α,α-disubstituted *N*-acyl amino acids *(4)* afford the ketones *(5)* on oxidation with lead(IV) acetate[3] in hexamethylphosphoric triamide (HMPT)/tetrahydrofuran (THF) at 0—20°C (Table 1).



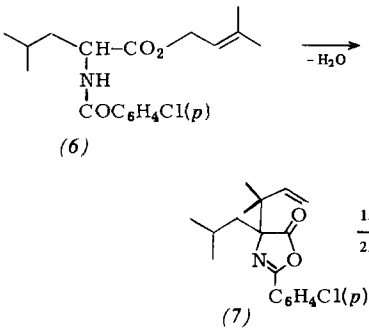
(1) *(2)* *(3)* *(4)* *(5)*

Table 1. Compounds prepared. *(3c)*, *(7)*, and *(10)* were used as the crude products; all the other compounds gave correct elemental analyses.

				Oxazolin-5-ones		*N*-Acyl amino acids			Ketones, aldehydes		
	R^1	R^2	R^3	Yield [%]	B.p. [°C/torr] [a]		Yield [%]	M.p. [°C] [b]		Yield [%]	B.p. [°C/torr] [a] (m.p. [°C])
(3a)	$C_6H_5CH_2$	C_6H_5	$(CH_3)_2C{=}CHCH_2$	87	208/0.05	*(4a)*	82 (crude)	174—177	*(5a)*	82	85/0.05
(3b)	$(CH_3)_2CH$	C_6H_5	*p*-Cl—$C_6H_4CH_2$	85	176/0.1	*(4b)*	70	210—212	*(5b)*	79	(57—59) [c]
(3c)	$(CH_3)_2CHCH_2$	*p*-Cl—C_6H_4	$(CH_3)_2C{=}CHCH_2$	95.5 (crude)	144/0.05	*(4c)*	74	144—146	*(5c)*	70	110/43 [d]
(7)				90	oil [e]	*(4d)*	67 [f]	156—158	*(8)*	78	70/18
(10)				98 (crude)	oil	*(4e)*	61 [g]	160—162	*(11)*	61	112/30 [h]

[a] Internal temperature of furnace on bulb-tube distillation. [b] From ethyl acetate. [c] Chromatographed on silica gel (CCl_4 eluent). [d] Semicarbazone, m.p. 69°C. [e] Rearranges on heating to 2-(*p*-chlorophenyl)-2-(1,1-dimethylallyl)-4-isobutyl-3-oxazolin-5-one [4a]. [f] Based on *(6)*. [g] Based on *(9)*. [h] Semicarbazone, m.p. 168—170°C.

Since 4-allyl substituted oxazolinones *(3)* are also accessible by dehydration of *N*-acyl amino acid allyl esters *via* Claisen rearrangement of the intermediate 5-allyloxyoxazoles[4], the scope of the new ketone synthesis is considerably enhanced. Thus, *N*-(*p*-chlorobenzoyl)leucine 3-methyl-2-butenyl ester *(6)* reacts with $PPh_3/C_2Cl_6/NEt_3$ in acetonitrile[5] at 0°C to give the oxazolinone *(7)*[6], which, after ring opening[7], can be oxidized to give the ketone *(8)* in good yield.



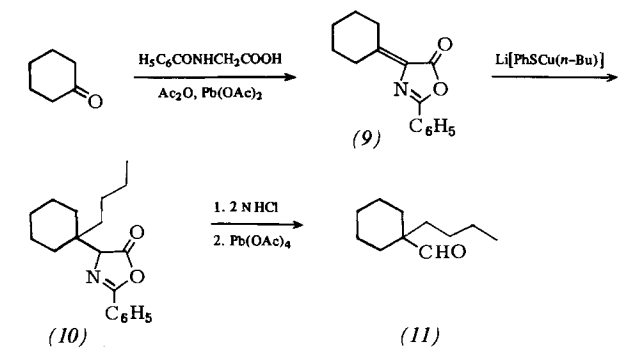
(6) *(7)* *(8)*

Allyl hippurates can react further to give 5-chlorooxazoles; in this case it is better to use the corresponding *N*-acylaminomalonic ester as starting material[8].

Oxidative cleavage of oxazolinones also permits a facile synthesis of aldehydes from carbonyl compounds according to

$$R^1R^2C{=}O \rightarrow R^1R^2R^3C{-}CHO$$

For example, cyclohexanone reacts with hippuric acid/acetic anhydride/lead(II) acetate[9] according to *Erlenmeyer* to form 4-cyclohexylideneoxazolinone *(9)*, which smoothly affords the oxazolinone *(10)*[11] on treatment with lithium phenylthio-*n*-butylcuprate[10]. After ring opening, *(10)* can be oxidized to the aldehyde *(11)* in 61 % yield.



(9) *(10)* *(11)*

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Procedure

Hydrolysis of *(3)*: Crude *(3)* obtained by alkylation[2] of *(2)* (50 mmol) is stirred overnight in ether (100 ml) with 30% caustic soda (20 ml). After hydrolysis (TLC check) the aqueous phase is acidified with 2 N HCl and extracted with $CHCl_3$. The organic phase is washed with water, dried, and evaporated down. The residue is recrystallized from ethyl acetate. Alternatively, *(3)* can be hydrolyzed overnight with 2 N HCl (10 ml) in acetone (30 ml). After stirring with saturated $NaHCO_3$ solution (500 ml) and light petroleum (100 ml), the aqueous phase is acidified and worked up as above (concerning the hydrolysis of oxazolinones subject to strong steric hindrance, such as *(7)*, see ref. [7]).

Lead(IV) acetate oxidation: To a stirred solution of *(4)* (10 mmol) in HMPT (4 ml) and anhydrous THF (24 ml) at 0°C is added lead(IV) acetate (4.65 g, 10.5 mmol). As soon as the initially vigorous evolution of CO_2 subsides, the ice bath is removed and the mixture is allowed to warm up to 20°C. Once the reaction is complete (amount of CO_2, TLC check) the resulting *N*-acylketimine is hydrolyzed by addition of water (60 ml) and oxalic acid dihydrate (13 g) or 20% hydrochloric acid (50 ml) [*(5b)*, *(8)*] and the mixture is stirred for 2 h with light petroleum (40—60°C) (30 ml). The organic phase affords the carbonyl compound on drying and evaporation; it is purified by vacuum distillation or filtration through a silica gel column (CCl_4 as eluent).

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$Ce_4O_4S_3$: A Mixed-Valence Cerium Oxide Sulfide

By *Winfried Wichelhaus*[*]

According to *Marcon*[1], oxide sulfides $M_4O_4S_3$ exist for M = Ce, Np, and Pu. These compounds are reported to contain the metals as M^{3+} and M^{4+} ions and to crystallize in a pseudohexagonal superstructure of Ce_2O_2S. The conditions for synthesis and the crystal structure have not yet been reported.

The author's own systematic studies on oxide sulfides of rare earth metals showed that single crystals of $Ce_4O_4S_3$ can be prepared by reaction of CeO_2 with Ce_2S_3 in a NaCl/KI melt. The crystal structure was solved from four-circle diffractometer data (499 reflections with $I > 2\sigma(I)$) and refined to $R = 0.031$ for isotropic temperature factors. $Ce_4O_4S_3$ forms orthorhombic crystals, space group Pbam (no. 55), with $a = 6.856$, $b = 14.558$, $c = 3.984$ Å; $Z = 2$; $d_{calc} = 6.073$, $d_{exp} = 6.04$ g/cm³. The atoms occupy the positions listed in Table 1.

Table 1. Positional parameters and temperature factors of $Ce_4O_4S_3$.

Atom	Position	x	y	z	B [Å²]
Ce(1)	4 g	0.2180	0.1618	0	0.39
Ce(2)	4 h	0.2880	0.4225	½	0.32
S(1)	2 c	0	½	0	0.48
S(2)	4 h	0.0126	0.2812	½	0.39
O(1)	4 g	0.3746	0.3762	0	0.69
O(2)	4 h	0.1351	0.0694	½	0.48

The structure of $Ce_4O_4S_3$ contains $[Ce_4O_4]^{6+}$ units one-dimensionally linked along [001] and joined by common S^{2-} ions. It cannot be described as a superstructure of Ce_2O_2S[2] which would contain layers of $[Ce_2O_2]^{2+}$ and S^{2-}

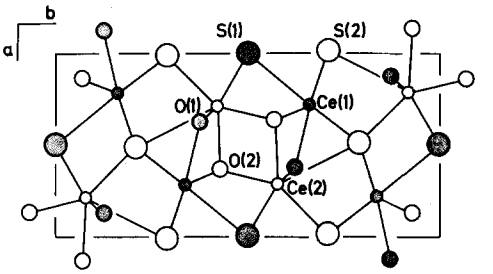


Fig. 1. Crystal structure of $Ce_4O_4S_3$; solid circles for $z = 0$, open circles for $z = ½$.

The Ce in $Ce_4O_4S_3$ occupies two crystallographically distinct positions. These differ significantly in their coordination by anions; distances {number}: Ce(1)—O = 2.42—2.46 Å {3}, Ce(1)—S = 2.98—3.05 Å {5}; Ce(2)—O = 2.17—2.38 Å {4}, Ce(2)—S = 2.79—3.34 Å {4}. Assignment of valence is possible on the basis of the shortest bond lengths. $Ce_4O_4S_3$ is the first reported mixed-valence oxide sulfide of rare earth metals, containing both Ce^{3+} [Ce(1)] and Ce^{4+} [Ce(2)]. In agreement with its formulation as $Ce^{III}Ce^{IV}_2O_4S_3$, it exhibits paramagnetic behavior ($\theta = -42$ K; $\mu_{exp}/\mu_B = 2.48$, based on Ce^{3+}). The compound is a semiconductor. Isotypic oxide sulfides $Ln^{III}M^{IV}_2O_4S_3$ could be prepared by replacement of Ce^{3+} by Ln^{3+} (Ln = Gd—Lu, Y) and of Ce^{4+} by M^{4+} (M = Zr, Hf): *e.g.* $Y_2Zr_2O_4S_3$ with $a = 6.520$, $b = 14.196$, $c = 3.680$ Å[3].

Experimental

CeO_2 (860.6 mg, 5 mmol), Ce_2S_3 (940.6 mg, 2.5 mmol), and S (80 mg) were melted together with a eutectic mixture of NaCl/KI (5 g) in an evacuated quartz ampoule (i.d. 15 mm, *l* 100 mm). The horizontal ampoule was heated in a two zone furnace (600—550°), the reactants being located in the higher temperature zone. After several days' heating, black needles of $Ce_4O_4S_3$ were formed. Relatively large single crystals were found in the colder part of the ampoule. The solidified melt was dissolved in water, filtered, and the residual cerium oxide sulfide freed from excess S by washing with CS_2. $Ce_4O_4S_3$ decomposes above 730°C *in vacuo* with separation of S; highly pure Ce_2O_2S is formed. The reaction is reversible.

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CAS Registry numbers:
$Ce_4O_4S_3$, 12442-50-1; CeO_2, 1306-38-3; Ce_2S_3, 12014-93-6

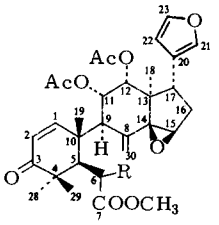
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Toonacilin and 6-Acetoxytoonacilin, Two Novel B-*seco*-Tetranortriterpenoids with Antifeeding Activity[**]

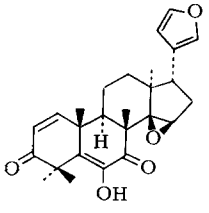
By *Wolfgang Kraus*, *Wolf Grimminger*, and *Gisela Sawitzki*[*]

Several types of shrubs and trees of the Meliaceae family are rarely attacked by insects; extracts from the leaves or fruits of these plants can be used as pesticides for the protection of other plant varieties[1]. So far, azadirachtin[2] from *Azadirachta indica* A. Juss and meliantriol[3] from *Melia azederach* L. are already known to be active anti-feeding principles. Extracts from leaves of *Toona ciliata* M. J. Roem. *var. australis* exhibit a strong antifeeding and insecticidal activity on the moth *Hypsipyla grandella* Zeller (Lep., Pyralidae)[4] and the Mexican bean beetle *Epilachna varivestis* Muls. (Coleoptera, Coccinellidae)[1]. The latter is known as a virulent pest in soybean plantations in America. We report here on the isolation and structural elucidation of two novel compounds from the bark of *Toona ciliata* which act as feeding repellents to *Epilachna varivestis*[5].

The two compounds, for which we have suggested the names toonacilin *(1)* and 6-acetoxytoonacilin *(2)*, are the first B-*seco*-tetranortriterpenoids with an intact Ring A which are related to cedrelone *(3)*.



(1), R = H
(2), R = OAc



(3)

Isolation: After repeated column chromatography on silica gel the ether extract from 20.8 kg of powdered bark[6] yielded 12 g of a fraction containing toonacilin. From methanolic solution there first precipitated 1 g of a 1:1 mixture of crystals of *(1)* and *(2)* (prisms, m.p. 151—152 °C). After concentration by evaporation, the mother liquor afforded 7 g of pure *(1)* (needles, m.p. 118—119 °C, $[\alpha]_D^{20} = +69°$ ($CHCl_3$, $c = 1$ g/100 ml)). Preparative high-pressure liquid chromatography of the mixed crystals followed by crystallization from methanol gave 335 mg of pure *(2)* (prisms, m.p. 215 °C, $[\alpha]_D^{20} = +42.5°$ ($CHCl_3$, $c = 1$ g/100 ml)).

Structure of toonacilin (1): High resolution of the M^+ signal gave the mass 554.25097, thus indicating the empirical formula $C_{31}H_{38}O_9$ (calc. 554.25159); *R* value 13. The ^{1}H-NMR spectrum [in $CDCl_3$, δ referred to TMS = 0] shows four methyl groups (0.97, 3H; 1.01, 3H; 1.09, 6H), two acetoxy groups (1.79 and 1.99), one methyl ester group (3.65), one *exo*-methylene group (5.21 and 5.39, $J_{gem} = 1.0$ Hz), an isolated six-membered ring enone system (6.18 and 7.24, d, $J_{AB} = 10.4$ Hz) and a furan ring (6.16, 7.12 and 7.31). It follows from signals at δ = 5.34 and 5.36 that the two acetoxy groups are bound to secondary C atoms in a vicinal *cis* arrangement. The broad singlet at δ = 3.94 indicates an ether function. The ^{13}C-NMR spectrum (Table 1) shows three quaternary C atoms (δ = 41.9, 44.7, 46.0). The remaining ^{13}C-NMR signals were completely assigned by selective ^{1}H-^{13}C decoupling (IR and mass spectra, see Table 2).

From these structural units and assumption of biogenesis by oxidative ring opening of a 14,15-epoxymeliacane[7] [*(3)* or a precursor thereof] toonacilin was assigned the structure *(1)*. An isomeric C-*seco* structure can be be ruled out since the ^{1}H-NMR signal for H^{17} in *(1)* (δ = 2.94) is hardly shifted compared to that in *(3)*. The base peak in the mass spectrum (*m/e* = 209), formed by scission of the C^9—C^{10} bond, likewise provides evidence for structure *(1)*. The configuration at C^5, C^9, C^{11}, and C^{12} followed from decoupling experiments in the 360-MHz ^{1}H-NMR spectrum[8].

Table 1. ^{13}C-NMR data of compounds *(1)* and *(2)* (23 MHz, $CDCl_3$, δ rel. to TMS = 0).

C-Atom	*(1)*	*(2)*	C-Atom	*(1)*	*(2)*
1	151.8 d	150.2 d	18	14.3 q	14.2 q
2	126.7 d	127.0 d	19	20.0 q	19.5 q
3	202.5 s	202.0 s	20	122.9 s	122.8 s
4	46.0 s [a]	46.7 s [a]	21	140.1 d	140.1 d
5	44.3 d	47.2 d	22	111.5 d	111.5 d
6	31.9 t	71.1 d	23	142.3 d	142.3 d
7	174.0 s	170.8 s	28	23.0 q [b]	25.2 q
8	135.7 s	135.2 s	29	22.7 q [b]	21.5 q
9	57.2 d	57.6 d	30	120.7 t	121.2 t
10	44.7 s [a]	44.7 s [a]	—C(O)—OCH_3	51.9 q	52.5 q
11	74.6 d	74.6 d	—$OC(O)CH_3$	20.6 q	20.4 q
12	70.3 d	70.0 d		20.8 q	20.7 q
13	41.9 s	42.7 s		—	20.9 q
14	72.4 s	72.3 s	—$OC(O)CH_3$	168.9 s	168.6 s
15	60.3 d	60.2 d		169.7 s	169.5 s
16	32.8 t	32.8 t		—	170.0 s
17	38.6 d	38.7 d			

[a, b] Assignments may be interchanged.

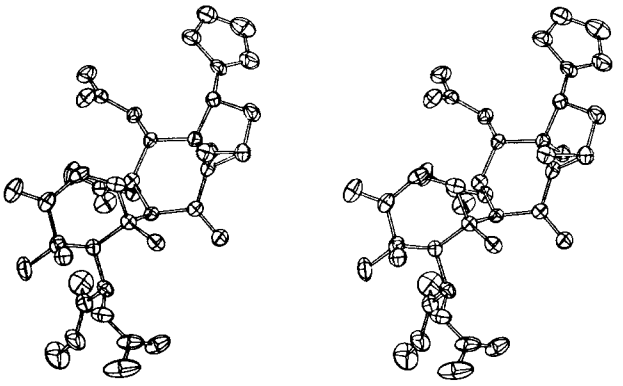


Fig. 1. Crystal structure of 6-acetoxytoonacilin *(2)* (ORTEP diagram). *(2)* crystallizes orthorhombically, space group $P2_12_12_1$-D_2^4, $a = 1327.5(6)$, $b = 989.1(3)$, $c = 2478.2(10)$ pm, $Z = 4$. Intensity measurements collected on a Syntex $P2_1$ four circle diffractometer (Mo-K_α radiation, ω scan, $T \approx 130$ K). On refinement (all H atoms included) the conventional *R* value converged to $R = 0.050$ for 2976 reflections with $I > 2\sigma(I)$.

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Table 2. IR- and MS data of compounds *(1)* and *(2)*.

(1), IR (KBr): 3165, 3145 (furan), 3082 (=CH_2), 3037 (=C—H), 1766, 1745 (ester carbonyl), 1688 (α,β-unsaturated six-membered ring ketone), 1504 (furan), 1247 (C—O), 881 and 874 cm^{-1} (furan and =CH_2)

(1), MS: m/e = 554 (3.8%, M^+), 494 (7.6%), 476 (2.2%), 434 (9.2%), 346 (9.8%), 345 (8.7%, Ring-C-D fragment), 225 (39%), 209 (100%, Ring-A fragment), 208 (78%), 177 (40%), 121 (52%)

(2), IR: essentially the same as the spectrum of *(1)*

(2), MS: m/e = 612 (2%, M^+), 552 (2.6%), 492 (2.5%), 432 (1.5%), 345 (5.9%, Ring-C-D fragment), 267 (74%, Ring-A fragment), 225 (32%), 207 (100%, Ring-A fragment −60), 175 (18%), 137 (34%), 121 (15%)

Structure of 6-acetoxytoonacilin (2): From the greater mass of *(2)* compared to that of *(1)* (a difference of m/e = 58), an additional acetoxy signal at δ = 2.21, a —CH—O signal at δ = 5.31, and the simplification of the H^5 signal in the ^{1}H-NMR spectrum with hardly any other alteration in the pattern of the signals, it was concluded that *(2)* must be the acetoxy derivative of *(1)*. The structure and stereochemistry of *(2)* were confirmed by X-ray structural analysis (Fig. 1).

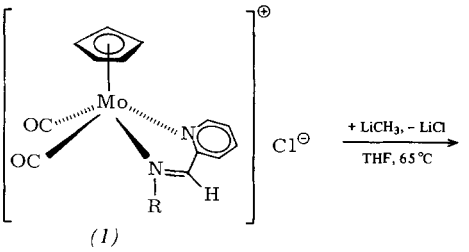
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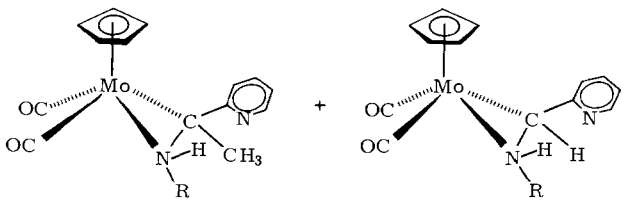
Ring Contraction in the Reaction of Cationic $C_5H_5Mo(CO)_2$ Chelate Complexes with Methyllithium

By *Henri Brunner, Heinrich Schwägerl, Joachim Wachter, George M. Reisner*, and *Ivan Bernal*[*]

A stereospecific phenyl addition at the azomethine carbon has been proposed to occur in the reaction of C_6H_5Li with $[C_5H_5Mo(CO)_2NN']PF_6$ (NN' = Schiff base derived from 2-pyridinecarbaldehyde and (*S*)-1-phenylethylamine)[1]. It has now been shown that reaction of CH_3Li with $[C_5H_5Mo(CO)_2NN']PF_6$ surprisingly results in a contraction of the five-membered chelate system present in the complex[2]. The rearrangement, which has been proved by IR, ^{1}H- and ^{13}C-NMR spectra as well as X-ray structure determination, involves several steps which can formally be considered as exchange of CH_3 for H at the azomethine carbon, addition of H to the imine nitrogen, cleavage of the Mo—N(pyridine) bond, and formation of a Mo—C bond to give a three-membered ring.



(1)



(2) *(3)*

R = CH_3, C_6H_5, $CH(CH_3)_2$, $CH_2C_6H_5$, $CH(CH_3)C_6H_5$

The cationic pyridinecarbaldimine complexes *(1)* react with excess CH_3Li to give the neutral compounds *(2)* and *(3)*. A strong N—H stretching vibration in the IR spectrum corresponds in the ^{1}H-NMR spectrum to a N*H*—C*H* coupling in the *N*-alkyl group of *(2)* and *(3)* and a N*H*—C*H* coupling within the three-membered ring of *(3)*, both of which collapse on addition of D_2O. In the complexes *(2)* the methyl substituent introduced gives a singlet. The structural relationship of both types of complexes *(2)* and *(3)* also is apparent from the similar ^{13}C-NMR spectra.

Compound *(2)* with R = $CH(CH_3)C_6H_5$ forms orange monoclinic crystals (space group $P2_1/a$) with cell constants a = 17.053(9), b = 11.185(5), c = 11.011(3) Å, β = 104.48(3)°; V = 2033.5 Å^3, d_{calc} = 1.44 g·cm^{-3}, Z = 4. From 6364 measured reflections ($Mo_{K\alpha}$ radiation, λ = 0.71069 Å) 3268 were used for the refinement of the structure (R value 5.4%). The dominant structural feature of the molecule is a η^2-aminomethylene ligand with *trans* arrangement of the large pyridyl and 1-phenylethyl substituents. In accord with exclusive for-

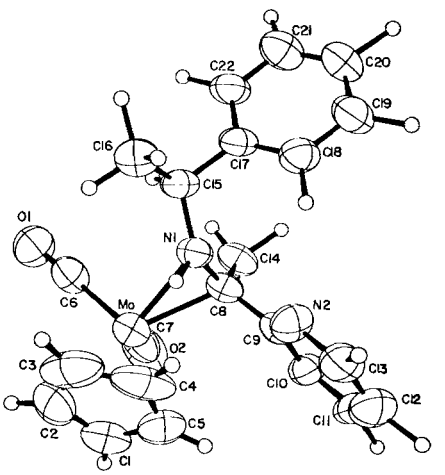


Fig. 1. ORTEP plot of *(2)*, R = $CH(CH_3)C_6H_5$. Bond lengths: Mo—N1 2.178(8), Mo—C8 2.223(12), C8—N1 1.418(16), Mo—C6 1.933(12), Mo—C7 1.932(13), Mo—Cp 2.348—2.407, C—C(phenyl and pyridyl ring) 1.381—1.415, C—N(pyridyl ring) 1.356(17), and 1.344(13) Å. Bond angles: N1—Mo—C8 37.6(4), N1—Mo—C6 92.3(4), C6—Mo—C7 78.4(6), C7—Mo—C8 78.9(5), Mo—N1—C8 72.9(6), Mo—C8—N1 69.5(6)°.

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mation of the *trans* structure, the NMR spectra of *(2)* and *(3)* each exhibit only one set of signals.

Compounds *(2)* and *(3)* correspond to a previously described complex type[3]; distances and angles in the three-membered ring of *(2)* are comparable with those in $(CO)_4MnCH_2NR_2$[4].

Procedure

To a suspension of *(1)* (5.6 mmol) in THF (100 ml) is added dropwise at room temperature $LiCH_3$ (11.2 mmol) in diethyl ether. The reaction is completed by 30 minutes' heating under reflux. On chromatography over SiO_2 with benzene $[C_5H_5(CO)_3Mo]_2$ is first eluted, then *(2)*, and on addition of some ether also *(3)*. The products were recrystallized from ether/pentane at −35 °C. Yields of *(2)* and *(3)* are 3—23%, depending on the substituents R.

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$[Fe_2(NO)_6]^{2+}$, A Binary Nitrosyliron Cation[**]

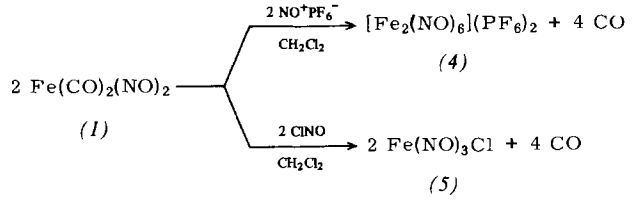
By *Max Herberhold* and *Reinhard Klein*[*]

In the isoelectronic series of tetrahedral carbonyl(nitrosyl)-iron complexes $[Fe(CO)_{4-n}(NO)_n]^{n-2}$ ($n=0$—4), the cationic members *(2)* and *(3)* have so far not been reported:

$Fe(CO)_4^{2-}$ $Fe(CO)_3(NO)^-$ $Fe(CO)_2(NO)_2$ *(1)*

$\{Fe(CO)(NO)_3^+\}$ *(2)* $\{Fe(NO)_4^{2+}\}$ *(3)*

We attempted the preparation of *(2)* by reaction of the neutral complex *(1)* with $NO^+PF_6^-$ and found that even less than an equimolar amount of the nitrosyl salt effects cleavage of both CO ligands from the complex, leading to formation of the deep-green salt $[Fe_2(NO)_6](PF_6)_2$ *(4)*. This oxidation of *(1)* corresponds formally to the known[1] formation of the mononuclear complex $Fe(NO)_3Cl$ *(5)* from *(1)* and nitrosyl chloride.



The new compound *(4)* is also obtainable by removal of halide from *(5)*:

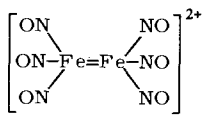
$$2\,(5) + 2\,AgPF_6 \xrightarrow[CH_2Cl_2]{} (4) + 2\,AgCl$$

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Particularly noteworthy, however, is the reaction of iron powder with $NO^+PF_6^-$ in nitromethane, which also leads to *(4)* without passage of NO gas.

We assume that the cation of the green salt *(4)* has a binuclear structure in which the iron atom achieves a noble gas configuration:



This structure is in agreement with the experimental findings on nitromethane solutions of *(4)*:

1. The ^{1}H-NMR spectrum reveals diamagnetism.
2. The equivalent conductivity ($\Lambda_e = 148 \pm 2\,cm^2/\Omega \cdot mol$ of a 10^{-3} M solution at −25.5 °C) lies within the range (150—180 $cm^2/\Omega \cdot mol$) typical for 2:1 electrolytes[2].
3. The Mössbauer spectrum[3] of a frozen solution ($\delta = 0.33$ mm/s, $\Delta E_Q = 0.49$ mm/s rel. to Fe metal; −196 °C) is reconcilable with only one sort of iron atoms.
4. The IR spectrum gives no indication of the presence of bridging nitrosyl ligands. The pattern of the two NO stretching absorptions corresponds to that expected for terminal nitrosyl groups (A+E). However, it remains unclear whether the NO ligands of both $[Fe(NO)_3]$-cation halves have D_{3d} (staggered) or D_{3h} (eclipsed) symmetry.

The salt *(4)* is stable only below −20 °C. It can be handled in polar solvents not having coordinating properties (CH_2Cl_2, $CHCl_3$); it is readily soluble in nitromethane. On addition of tetraalkylammonium halides, $NR_4^+X^-$, characteristic ν(NO) bands[4] of $Fe(NO_3)X$ (X = Cl, Br, I) appear in the IR spectrum. Phosphanes react with *(4)* to give adducts of the type $[Fe(NO_3)L]PF_6$ which behave like 1:1 electrolytes (*e.g. (6)*, L = PPh_3: $\Lambda_e = 82\,cm^2/\Omega \cdot mol$ in CH_3NO_2 at −25.5 °C).

Table 1. IR spectra in nitromethane solution (in cm^{-1}).

$Fe(CO)_2(NO)_2$	*(1)*	ν(NO) 1805 s, 1765 s;	ν(CO) 2095 s, 2043 s
$[Fe_2(NO)_6](PF_6)_2$	*(4)*	1937 w, 1828 s	
$Fe(NO)_3Cl$	*(5)*	1898 w, 1790 s	
$[Fe(NO)_3PPh_3]PF_6$	*(6)*	1919 m, 1828 s	
$[Fe(NO)_3PMe_3]PF_6$	*(7)*	1917 m, 1824 s	

Cationic nitrosylmetal complexes are of interest for investigations of catalysis[5]. Hexanitrosyldiiron(2+) is the first example of a binary nitrosylmetal cation.

Experimental[6]

(4): $NO^+PF_6^-$ (0.77 g, 4.4 mmol) is added to a solution of $Fe(CO_2)(NO)_2$ (0.52 g, 3 mmol) in dichloromethane (20 ml) and the mixture stirred for 2 h (evolution of gas), cooled to −30 °C, and filtered under N_2 pressure through a cold (−30 °C) frit. The dark-green residue consisting of *(4)* and unchanged $NO^+PF_6^-$ is washed with CH_2Cl_2 (2 × 30 ml) and the combined washings and filtrate slowly cooled to −78 °C. The dark-green fibrous needles which crystallize out are washed several times with pentane (−40 °C) and dried for 3 h at −78 °C/10^{-2} torr. Yield 0.08—0.10 g (*ca.* 10%).

(6): $NO^+PF_6^-$ (0.35 g, 2 mmol) is added portionwise to a stirred solution of *(1)* (0.34 g, 2 mmol) in nitromethane (20 ml) at −30 °C. When evolution of CO has ceased (after *ca.* 5 min), a cold (−30 °C) solution of triphenylphosphane (0.54 g, 2 mmol) in nitromethane is added dropwise to the mixture. On subsequent addition of cold toluene lustrous green leaflets of *(6)* crystallize out which are then washed at −30 °C with

toluene and pentane, recrystallized from CH_3NO_2/Et_2O, and finally dried in a high vacuum; dec. pt. 118°C (in N_2-filled capillary tubes). Yield 80–90%.

The trimethylphosphane complex $[Fe(NO_3)PMe_3]PF_6$ *(7)* is formed in an analogous way, dec. pt. 143°C.

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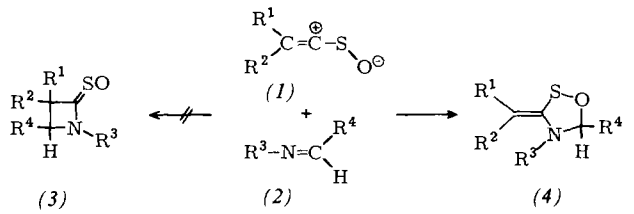
CAS Registry numbers:
(1), 13682-74-1; *(4)*, 66523-75-9; *(5)*, 14972-71-5; *(6)*, 66552-49-6; *(7)*, 66523-68-0

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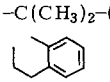
γ-Sultenes and 1,3-Oxazolidinethiones by 1,3-Dipolar Cycloaddition of Thioketene *S*-Oxides to Azomethines[**]

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Thioketenes undergo [2+2] cycloadditions with azomethines to give β-thiolactams[1]. The analogous β-thiolactam *S*-oxide structure is ruled out for the 1:1 adduct of thioketene *S*-oxide *(1b)*[2a] and the azomethine *(2a)* because, in contrast to independently synthesized compounds *(3)*[2b], the product fails to show a *S*-oxide band in the IR spectrum. The spectroscopic data (Table 1) are in accord with the structure of a 1,2,4-oxathiazolidine *(4)*, *i.e.* a representative of the still largely unknown[3] cyclic esters of sulfenic acid (sultenes). Thus *(1)* surprisingly reacts as a 1,3 dipole[4a]. Although a dipolar resonance structure has been considered in the description of the ground state of other thiocarbonyl oxides[4b], it has not previously been detected in reactions.



(3) *(1)* *(2)* *(4)*

(1a), *(4a)*-*(6a)*: $R^1 = CH(CH_3)_2$, $R^2 = C(CH_3)_3$
(1b), *(4b,c)*-*(6b,c)*: $R^1 + R^2 = -C(CH_3)_2-(CH_2)_3-C(CH_3)_2-$
(2a), *(4a,b)*-*(6a,b)*: $R^3 + R^4 =$ 
(2b), *(4c)*-*(6c)*: $R^3 = CH_3$, $R^4 = C_6H_5$

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Table 1. Reaction conditions, yields, and principal IR bands of *(4)*, *(6)*.

	T [°C]	Reaction time	Solvent	Yield [%]	M.p. [°C]	IR (KBr) [cm⁻¹]
(4b)	25	1 d	Ether	70 [a]	97—98 [b]	1575(C=C)
(6a)	25	12 h	Ether	58 [c]	103—105	1485(Thioamide-B)
(6b)	40	6 h	None	72 [c]	96—97	1480(Thioamide-B)
(6c)	55	10 d	None	48 [c]	94—95	1485(Thioamide-B)

[a] *(4b)* crystallizes from a small volume of diethyl ether. [b] On melting *(4b)* undergoes partial conversion into *(6b)*. [c] Isolated by preparative layer chromatography on silica gel (Kieselgel PF 254, eluent dichloromethane/light petroleum or ethyl acetate/light petroleum).

X-Ray structure analysis[5] of *(4b)* confirms the proposed structure (cf. Fig. 1). The bond lengths in the C—S—O—C moiety largely correspond to the values already measured for an open chain sulfenic ester, while the angles at the sulfur and the nitrogen are *ca.* 6° smaller[6]. The oxathiazolidine ring exists in an envelope conformation, with C-5 deviating from the plane of the other ring atoms (±8 pm).

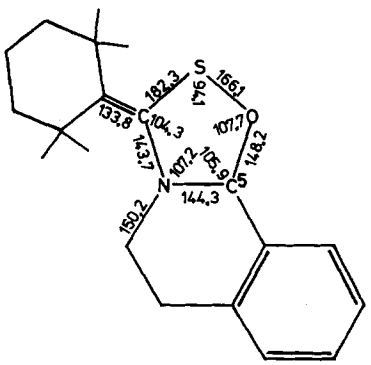
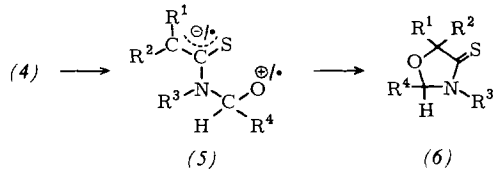


Fig. 1. Principal bond lengths [pm] (standard deviation 0.7 pm) and angles [°] (standard deviation 0.4°) in γ-sultene *(4b)*.

The oxathiazolidines *(4a)* and *(4c)* cannot be obtained in pure form by reaction of *(1a)* with *(2a)* or of *(1b)* with *(2b)* because rearrangement to the 1,3-oxazolidine-4-thiones *(6)* competes with formation of *(4)*.



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

The structure of the isomerization products has been proved by X-ray analysis in the case of *(6c)*[7]. The crystalline product *(4b)* is also unstable in solution, rearranging *via* rupture of the SO bond with a half-life of 14 h (at 52°C in $CDCl_3$) to *(6b)*; a 1,5 dipole or 1,5 diradical *(5)* is assumed as intermediate. Rearrangement of the sultenes *(4)* is apparently favored by the absence of neighboring groups with hetero atoms, in contrast to other heterocycles with the SO structural unit[3b,8], which precludes stabilization by no-bond resonance[9].

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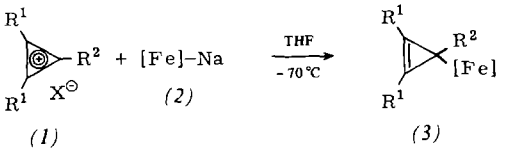
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[5] $a=1200.7(3)$, $b=822.8(3)$, $c=1894.0(15)$ pm, $\beta=98.27(5)°$ space group $P2_1/a$, $Z=4$; 1605 independent reflections ($F>3\sigma$); $R=0.060$. Recorded by the $\theta/2\theta$ scan technique on a four-circle single crystal diffractometer (Syntex $P2_1$) with monochromatic $Cu_{K\alpha}$ irradiation. Solved by direct methods (Multan). We are indebted to Dr. *Th. Greiser* for determining the crystal parameters.
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σ-Dicarbonylcyclopentadienyliron Derivatives of Cyclopropenes and Cyclopropenylium Salts[**]

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We have synthesized dicarbonyl(η-cyclopentadienyl)(1,2,3-triphenylcyclopropenyl)iron *(3a)* as a potential masked cyclopropenyl anion from triphenylcyclopropenylium salts *(1a)* and sodium dicarbonyl(cyclopentadienyl)ferrate *(2)*[1]. However, *(3a)* does not react as a cyclopropenyl anion with electrophiles[1]. In order to establish whether cyclopropenyl-[Fe]



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

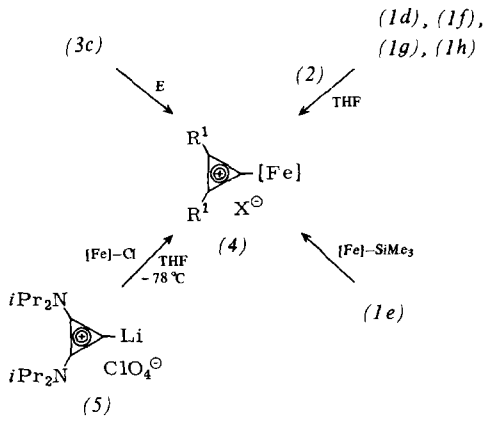
(1a), R^1, R^2 = Ph, $X=BF_4$, Br
(1b), R^1 = tBu, R^2 = Me, $X=ClO_4$
(1c), R^1 = Ph, R^2 = H, $X=ClO_4$
(1d), R^1 = tBu, $R^2=OCH_3$, $X=FSO_3$ [2]
(1e), R^1 = Ph, R^2 = Cl, $X=BF_4$
(1f), R^1 = Ph, $R^2=OCH_3$, $X=FSO_3$
(1g), $R^1=Et_2N$, R^2 = Cl, $X=ClO_4$
(1h), $R^1=iPr_2N$, R^2 = Cl, $X=ClO_4$

(3a), R^1, R^2 = Ph
(3b), R^1 = tBu, R^2 = Me
(3c), R^1 = Ph, P^2 = H

[Fe] = [Fe(C5H5)(CO)2]

derivatives act as synthetic equivalents of cyclopropenyl anions we have now prepared the derivative *(3b)* [yellow crystals; ^{1}H-NMR (CS_2): $\delta=1.18$ (s, 18H), 1.49 (s, 3H), 4.67 (s, 5H)] from *(1b)* and *(2)*. Compound *(3b)* is highly decomposable; it reacts similarly to *(3a)* with iodine in dichloromethane at −70 °C to form di-*tert*-butyl(methyl)cyclopropenylium pentaiodide (67 %) and [Fe]-I (*ca.* 60 %). *Green et al.*[3] obtained only dimers from *(1b)* and *(2)*.

Reaction of *(1c)* and *(2)* gives a 45 % yield of dicarbonyl(η-cyclopentadienyl)(2,3-diphenylcyclopropenyl)iron *(3c)* [IR (CS_2): 3063, 3055, 2840 (CH), 1995, 1937 (C≡O), 1782 cm^{-1} (cyclopropene); ^{1}H-NMR (CS_2): $\delta=2.63$ (s, 1H), 4.59 (s, 5H), 7.15—7.5 (m, 6H), 7.55—7.8 (m, 4H)]. It is much more stable than *(3b)* but less so than *(3a)*. The reactions of *(3c)* differ considerably from those of *(3a)*. All the electrophiles E tested so far (trityl tetrafluoroborate, $HOEt_2^+BF_4^-$, HCl, Br_2, I_2, $SbCl_5$, $(MeO)_3C^+BF_4^-$) give almost exclusively dicarbonyl(η-cyclopentadienyl)(σ-2,3-diphenylcyclopropenylidene)iron salts *(4c)* as pale yellow crystals [*(4c)*, $X=BF_4$: m.p. 185 °C (dec.); IR (KBr): 2045, 2005 (C≡O), 1368, 1330, 1310, 1288 cm^{-1} (three-membered ring); ^{1}H-NMR (CD_3CN): $\delta=5.55$ (s, 5H), 7.9 (mc, 6H), 8.3 (mc, 4H). *(4c)*, $X=ClO_4$: m.p. 183 °C (dec.). *(4c)*, X = Br: m.p. 175—180 °C (dec.). *(4c)*, $X=SbCl_6$: m.p. 188 °C (dec.)]. Compounds *(4c)* are structurally related with pentacarbonylchromium-[4a,5], pentacarbonylmolybdenum-[5], and palladium dichloride complexes[4b] of diphenylcyclopropylidene; the $PdCl_2$ complex of bis(diisopropylamino)cyclopropylidene can be transformed into a metallocyclopropenylium salt by treatment with antimony pentachloride[4c].



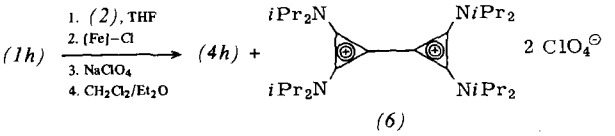
(5)

(4c), R^1 = Ph; *(4d)*, R^1 = tBu, $X=BF_4$
(4g), $R^1=Et_2N$, $X=ClO_4$; *(4h)*, $R^1=iPr_2N$, $X=ClO_4$

The complex salt *(4c)*, $X=BF_4$, is also obtained in *ca.* 50% yield on heating *(1e)* with dicarbonyl(cyclopentadienyl)(trimethylsilyl)ferrate[6] in dichloromethane or chloroform.

Other complex salts *(4)* arise from *(2)* and *(1d)*, *(1f)*, *(1g)*, or *(1h)*. In the case of *(1g)* and *(1h)*, some [Fe]—Cl is added on completion of reaction to remove excess *(2)*, followed by $NaClO_4$; in the case of *(1d)* and *(1f)* workup is performed with $HOEt_2^+BF_4^-$ [*(4d)*: 51 %, yellow crystals; m.p. 189—192 °C (dec.), IR (KBr): 2042, 2000 (C≡O), 1484, 1464, 1370, 1330 cm^{-1} (three-membered ring); ^{1}H-NMR ($CDCl_3$): $\delta=1.49$ (s, 18H), 5.41 (s, 5H), *(4g)*: 60 %, pale yellow crystals; m.p. 108—109 °C (dec.); IR (KBr): 2035, 1973 (C≡O), 1880, 1520, 1380, 1289 cm^{-1} (three-membered ring); ^{1}H-NMR ($CDCl_3$): $\delta=1.33$ (t, 12H), 3.55 (mc, 8H), 5.25 (s, 5H). *(4h)*: 8 %, light yellow crystals; m.p. 178—179 °C (dec.); IR (KBr): 2040, 1980 (C≡O), 1846, 1490, 1375, 1346, 1322 cm^{-1} (three-membered ring); ^{1}H-NMR ($CDCl_3$): $\delta=1.41$ (d, 24H), 4.15 (mc, 4H), 5.26 (s, 5H)]. Better yields (*ca.* 60 %) of *(4h)* than are obtained with *(1h)* and *(2)* [product also free from *(6)*] are achieved with dicarbonyl(cyclopentadienyl)iron chloride and the carbenoid *(5)*[7b] described by *Yoshida*.—The complex salts *(4)* are stable towards mineral acids.

Apart from the major product *(4h)* (42 %), reaction of *(1h)* with *(2)* affords the dication salt *(6)* [*(6)*·½ CH_2Cl_2: m.p. 260 °C (decrepitation); ^{1}H-NMR (CH_3CN): $\delta=1.31$ (d), 1.43 (d), 4.00 (sept), 4.20 (sept), 5.47 (s, CH_2Cl_2)].



(6)

Triafulvalene dication salts such as *(6)* were first obtained by *Yoshida*[8], and independently by *Weiss*[9].

Procedure

Synthesis of *(3a)*: A solution of *(2)* in tetrahydrofuran (THF) (10 ml), prepared from dimeric dicarbonyl(cyclopenta-

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[**] Donor/acceptor-substituted Aromatic Systems, Part 2.—Part *1*: [1].

dienyl)iron $[Fe]_2$ (1.7 g, 4.8 mmol) and 2% Na amalgam (*ca.* 17 g), was slowly added to a suspension of *(1c)* (2.6 g, 8.95 mmol) in THF (10 ml) cooled to −78 °C. After warming to −10 °C the solvent was removed in a high vacuum, the residue taken up in ether/dioxane 2:1 (15 ml), and the solution quickly filtered, after cooling to −10 °C, through a G3 frit. The filtrate was evaporated to dryness in high vacuum at −10 °C, the residue taken up in ether (10 ml), and the solution stirred for several hours at −40 to −70 °C. Cooling was continued and the yellow crystals were freed from supernatant liquor by means of an immersion frit, washed with ether, ether/hexane 1:1, and hexane (5 ml of each, cooled at −70 °C), and dried in a high vacuum. Yield 1.51 g (46%), m.p. 66—67 °C on rapid heating, decomposition.

Synthesis of *(4c)*, X = BF_4: A solution of [Fe]—$SiMe_3$[6] (2.5 g, 10 mmol) and *(1e)* (3 g, 9.6 mmol) in chloroform (50 ml) was refluxed for 1 h. After cooling to room temperature, the volatile components were removed in a high vacuum. The residue was taken up in CH_2Cl_2 (15 ml) and the resulting solution filtered. Ether (20 ml) was slowly added to the filtrate; the precipitate was recrystallized from CH_2Cl_2/ether. Yield 1.75 g (40%).

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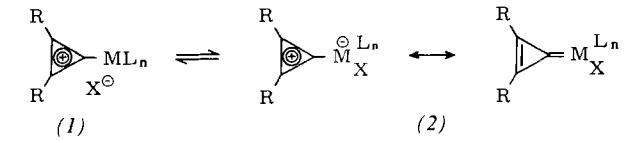
CAS Registry numbers:
(1a), 741-16-2; *(1b)*, 25339-22-4; *(1c)*, 37647-36-2; *(1d)*, 66633-50-9; *(1e)*, 66633-48-5; *(1f)*, 66633-47-4; *(1g)*, 32269-07-1; *(1h)*, 32269-08-2; *(2)*, 12152-20-4; *(3a)*, 66652-60-6; *(3b)*, 66652-59-3; *(3c)*, 66652-73-1; *(4c)* (X = BF_4), 66652-72-0; *(4c)* (X = ClO_4), 66652-71-9; *(4c)* (X = Br), 66652-70-8; *(4c)* (X = $SbCl_6$), 66652-69-5; *(4d)* (X = BF_4), 66652-67-3; *(4g)* (X = ClO_4), 66719-18-4; *(4h)* (X = ClO_4), 66687-75-0; *(5)*, 66652-65-1; *(6)*, 61695-57-6; [Fe]-$SiMe_3$, 31811-63-9; [Fe]-Cl, 12107-04-9

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[2] *(1d)* was obtained from di-*tert*-butylcyclopropenone and methyl fluorosulfate [very hygroscopic, ^{1}H-NMR ($CDCl_3$): δ = 1.47 (s, 18H), 4.60 (s, 3H); IR (CH_2Cl_2): 1865, 1505 cm^{-1}].
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[4] a) *K. Öfele*, Angew. Chem. *80*, 1032 (1968); Angew. Chem. Int. Ed. Engl. *7*, 900 (1968); J. Organomet. Chem. *22*, C9 (1970); c) *R. Weiss, C. Priesner*, Angew. Chem. *90*, 491 (1978); Angew. Chem. Int. Ed. Engl. *17*, 457 (1978); *C. Priesner*, Dissertation, Universität München 1977.
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[9] *R. Weiss*, personal communication (Dec. 21, 1977).

Coordinatively Unsaturated Transition Metal-Substituted Cyclopropenylium Systems[**]

By *Robert Weiss* and *Claus Priesner*[*]

We have examined the conditions under which coordinatively unsaturated transition metal-substituted species[1] *(1)* can exist.

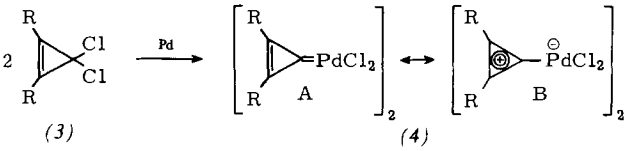


(1) *(2)*

ML_n = coordinatively unsaturated transition metal center

If the counterion $X^\ominus$ has ligand properties, it should be incorporated into the coordination sphere of M to form an electroneutral cyclopropenylidene complex *(2)*. With the aid of strong Lewis acids we have been able to transform compounds of type *(2)* into those of type *(1)*; the substituents R were found to exert a decisive influence.

We first synthesized complexes *(4a)*[2]—*(4c)* which are readily accessible in 60—70% yield from the dichlorides *(3)*[3] and Pd black according to *Öfele*[2].



(3) *(4)*

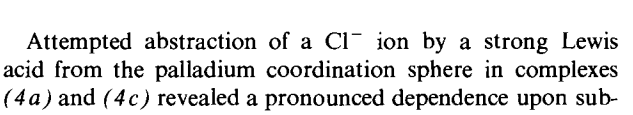
(a), R = C_6H_5; *(b)*, R = t-C_4H_9; *(c)*, R = $N(i\text{-}C_3H_7)_2$

The new carbene complexes *(4b)* and *(4c)* (Table 1) are orange-yellow, air-stable compounds showing considerable thermal stability, which, unlike *(4a)*, are readily soluble in polar solvents without pronounced donor character. Their IR spectra have the same habit as that of *(4a)* in the region of metal-halogen frequencies[2]. The IR and ^{1}H-NMR data of *(4b)* and *(4c)* are expectedly in accord with a large contribution from the resonance structure B.

Table 1. Characteristic data of the cyclopropenylidene complexes *(4b)* and *(4c)*.

	M.p. [°C]	IR (KBr) [cm^{-1}]	^{1}H-NMR δ	UV (CH_2Cl_2) λ_{max} [nm] (ε)
(4b)	225 (dec.)	1920 (m) 1480 (s) 1457 (s) 1396 (vs) 1383 (s)	1.47 (s) ($CDCl_3$, TMS)	
(4c)	185 (dec.)	1855 (m) 1500 (vs) 1455 (s) 1400 (m) 1374 (m)	4.0 (mc, 4H) 1.61/1.51 (d, J = 10 Hz, 24H) ([D_6-acetone, TMS)	325 (4100)

Attempted abstraction of a Cl^- ion by a strong Lewis acid from the palladium coordination sphere in complexes *(4a)* and *(4c)* revealed a pronounced dependence upon substituent R. Thus the action of $AgOSO_2CF_3$ on *(4a)* does not release AgCl, whereas AgCl is released gradually in the case of *(4b)* and instantaneously in the case of *(4c)*. No characteristic product of *(4b)* has been isolated; the desired reaction does, however, take place with *(4c)*.



R = i-C_3H_7 *(5)*

Compound *(5)* has so far only been isolated as amorphous material [m.p. >118 °C (dec.); IR (KBr): 1870 (s), 1525 (vs),

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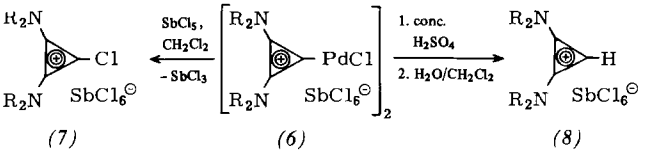
[**] Functional *cyclo*-C_3 Derivatives, Part 6. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 5: [1a].

1464 (m), 1408 (m), 1380 (m), 1345 (s) cm^{-1}; ^{1}H-NMR (CD_3CN)[5]: $\delta = 3.93$ (mc, 4H); 1.52/1.42 (d, $J = 10$ Hz, 24H)]. The ionic formulation of *(5)* follows from the characteristic IR absorption bands of the anion at 1030, 1140, 1270 cm^{-1}. The fragment of highest mass number ($m/e = 237$) corresponds to demetalation with formation of the cation *(8)*.

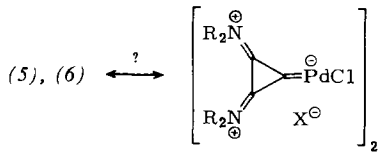
The complexes *(4a)*—*(4c)* show a similar gradation of reactivity towards $SbCl_5$. Thus *(4a)* does not react at all, *(4b)* only reluctantly and in still unknown manner, but *(4c)* combines instantaneously and quantitatively to give the hexachloroantimonate *(6)* corresponding to *(5)*.

Compound *(6)* is a yellow, air-stable crystalline salt (m.p. 185°C (dec.)); its ^{1}H-NMR spectrum (CD_3CN[5]) resembles that of *(5)*. Apart from anion-induced differences, its IR spectrum is also similar to that of *(5)*. The presence of a discrete $SbCl_6^-$ ion is evidenced by an intense IR band at 340 cm^{-1} (ν_{as})[6].

To our knowledge, *(5)* and *(6)* are the first coordinatively unsaturated transition metal-substituted cyclopropenylium systems[7]. Such species are expected to undergo demetalating S_E reactions[1a]. We have been able to confirm this for two model reactions: thus *(6)* can be subjected to electrophilic chlorination by $SbCl_5$, giving *(7)*[4], and to protonolysis by conc. H_2SO_4[8], giving *(8)*[4].



It seems logical to attempt to correlate the increasing tendency of palladium to release Cl^- in the series *(4a)*—*(4c)* with the donor properties of R[9] and thus with the increasing weight of the polar resonance structure B. The ready formation of *(5)* and *(6)* might possibly be rationalized by assuming the three-membered ring in *(5)* and *(6)* to act as a four-electron donor according to the [3]radialene resonance structure[10] C. Hindered rotation of the NR_2 substituent has not yet been detected by ^{1}H-NMR spectroscopy, possibly owing to the coordinating properties of the solvent CD_3CN.



If the formulations *(5)* and *(6)* correctly represent the structural situation, then the compounds are formally tricoordinate d^8 complexes[11]. Such 14-electron systems play an important role in homogeneous catalysis[11].

Procedure

Synthesis of *(6)*: A well stirred suspension of *(3c)* (612 mg, 2 mmol) and pretreated[2] Pd black (212 mg) in anhydrous benzene (35 ml) is refluxed for 2 h. The new precipitate is extracted with CH_2Cl_2 and the carbene complex *(4c)* precipitated with ether; yield 520 mg (63 %) of analytically pure *(4c)*. $SbCl_5$ (297 mg, 1 mmol) in CH_2Cl_2 (5 ml) is added dropwise at room temperature to a stirred solution of *(4c)* (411 mg, 0.5 mmol) in CH_2Cl_2 (5 ml). A crystalline precipitate of *(6)* is rapidly formed. After 20 minutes' stirring, anhydrous CCl_4 (10 ml) is added and the salt *(6)* filtered off; yield 700 mg (94 %).

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(3a), 2570-00-5; *(3b)*, 66633-01-0; *(3c)*, 66633-02-1; *(4a)*, 34390-60-8; *(4b)*, 66652-80-0; *(4c)*, 66446-50-2; *(5)*, 66652-79-7; *(6)*, 66652-78-6; *(7)*, 66633-04-3; *(8)*, 66633-06-5

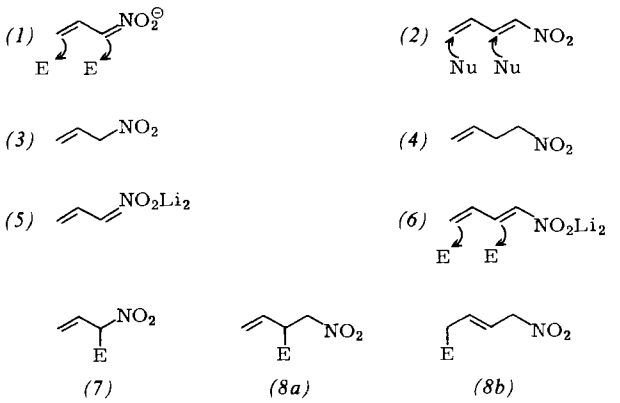
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[2] *K. Öfele*, J. Organomet. Chem. *22*, C9 (1970).
[3] The new dichlorides *(3b)* and *(3c)* were prepared by standard methods from the parent cyclopropenones; see *J. Ciabattoni, E. C. Nathan III*, J. Am. Chem. Soc. *90*, 4495 (1968); *Z. Yoshida, H. Konishi, Y. Tawara, H. Ogoshi, ibid. 95*, 3043 (1973); in contrast to *(3b)*, *(3c)* is a salt-like compound [4].
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[9] *Z. Yoshida*, Top. Curr. Chem. *40*, 47 (1973).
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Double Deprotonation of 3-Nitropropene and 4-Nitro-1-butene: Derivatives of Their Dianions as Novel Reagents for CC-Linkage

By *Dieter Seebach, Rainer Henning*, and *Friedrich Lehr*[*]

To our knowledge, C—C linkage reactions with the allylic nitronate *(1)* have not been reported in the literature; nucleophiles can add to the nitrobutadiene *(2)* in positions 2 or 4[1].

Under the reaction conditions previously described by us (2 equiv. of *n*-butyllithium at −80 to −90°C in THF containing HMPT)[2] for generation of simple nitroalkane dianions,



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Table 1. Products *(8a)* and *(8b)* of reaction of the dilithio derivative *(6)* with electrophiles. The isomer ratios were determined by ^{1}H-NMR spectroscopy or gas chromatography. The overall yield is the sum of the products isolated by chromatography or recrystallization. Separation G (gas chromatography, OV 101), C (column chromatography, SiO_2). The ^{1}H-NMR data refer to the α-NO_2—CH_2 signals [δ values, multiplicity (d, t, m), coupling constant in Hz].

No.	Electrophile [E in *(8)*]	Isomer ratio *(8a)/(8b)*	Overall yield [%]	Separation	^{1}H-NMR spectrum *(8a)*	*(8b)*
1	D_2O [D]	52/48	80 [a]	—	4.4 d (7)	4.8 d (7)
2	Iodomethane [CH_3]	40/60	71	G	4.2 m	4.83 d (6.9)
3	1-Iodooctane [n-C_8H_{17}]	12/88	75	G	4.22 d (7.5)	5.3 m
4	2-Iodopropane [$CH(CH_3)_2$]	≈3/97	53	S	—	4.82 d (6.6)
5	Bromocyclopentane [$CH(CH_2)_4$]	20/80	68	—	4.28 m	4.8 d (7)
6	Benzyl bromide [$CH_2C_6H_5$]	20/80	68	S	4.2 d (7)	4.85 d (7)
7	Pivalaldehyde [$(CH_3)_3CCH(OH)$]	52/48	65	G	4.4 m [b]	
8	Hexanal [n-$C_5H_{11}CH(OH)$]	56/44	76	S	4.5 m [b]	
9	Benzaldehyde [$C_6H_5CH(OH)$]	30/70	74	S	4.4 m [b]	4.67 d (6)
10	Cyclohexanone [$(CH_2)_5C(OH)$]	50/50	82	S	4.6 m	4.84 d (6)
11	Benzophenone [$(C_6H_5)_2C(OH)$]		42	S [c]		4.7 m
12	2-Cyclopenten-1-one [{—$(CH_2)_2$—CO—CH_2—}CH]		40	S		4.9 d (6.3)
13	2-Cyclohexen-1-one [{—$(CH_2)_3$—CO—CH_2—}CH]	only *(8b)*	48	S		4.92 d (6)
14	2-Cycloheptan-1-one [{—$(CH_2)_4$—CO—CH_2—}CH]		60	S		4.95 d (6)
15	Benzylideneacetophenone [$C_6H_5COCH_2CH(C_6H_5)$]		72	— [d]		4.8 m

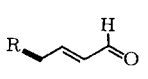
[a] According to ^{1}H-NMR, the 4-nitro-1-butene obtained is 74% deuterated in the β-position, and the 1-nitro-2-butene 83% deuterated in the γ position. [b] Mixture of diastereomers. [c] M.p. 66—68 °C. [d] M.p. 46—47 °C.

the allylic compound *(3)*[3] undergoes α,α double deprotonation to give *(5)*, whereas the homoallylic derivative *(4)*[4] yields dark red solutions of the α,β abstraction product *(6)*. This is shown by the reactions of *(5)* and *(6)* with *electrophiles*.

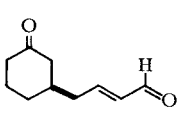
The C_3 nucleophile *(5)* reacts with acetone, cyclohexanone, benzaldehyde, and benzophenone at the α-nitro C atom to form nitro alcohols of type *(7)* [*(7a)*: E=$(CH_3)_2C(OH)$, 40%, b.p. 70 °C (bath)/0.3 torr, n_D^{20}=1.4588; *(7b)*: E=$(CH_2)_5C(OH)$, 60%, b.p. 90 °C (bath)/0.01 torr, n_D^{20}=1.4918; *(7c)*, E=$C_6H_5CH(OH)$, mixture of diastereomers, 70%, b.p. 120 °C/0.005 torr; *(7d)*: E=$(C_6H_5)_2C(OH)$, 53%, m.p. 75 °C]; their ^{1}H-NMR spectra show the multiplets expected for the vinyl groups[5].

The diene *(6)* affords the mixtures of the products *(8a)* and *(8b)* in the ratios and yields given in Table 1 (Nos. 1—11) on reaction with alkyl halides, aldehydes, or ketones. Separation can generally be accomplished by gas or column chromatography, and identification by the characteristic ^{1}H-NMR chemical shifts and coupling constants of the α-NO_2—CH_2 groups likewise listed in Table 1 [decoupling experiments with compounds *(8b)* give typical *trans* coupling constants of 13—17 Hz]. Interest attaches to the Michael additions (Nos. 12—15 of Table 1) which give the readily isolable products of δ attack on the π system *(6)*.

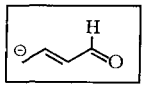
We have transformed three of the δ adducts *(8b)* into the α,β-unsaturated aldehydes *(9a)* and *(9b)* and into the



(9a), R = $CH(CH_3)_2$
(9b), R = $CH_2C_6H_5$



(10)



(11)

1,7-keto aldehyde *(10)*[7] by Nef reaction with $TiCl_3$[6] (Nos. 4, 6, and 13 in Table 1). Thus for synthetic purposes, *(6)* is not only a nitrobutadiene exhibiting umpolung [cf. *(2)*] but also a crotonaldehyde enolate equivalent [cf. *(11)*], which, unlike normal dienolates, preferentially reacts at the γ position to the carbonyl group and not at the α position.

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CAS Registry numbers:
(3), 625-46-7; *(4)*, 32349-29-4; *(5)*, 66538-49-6; *(6)*, 66538-50-9; *(7a)*, 66538-51-0; *(7b)*, 66538-52-1; *(7c)* (isomer A), 66538-53-2; *(7c)* (isomer B), 66538-54-3; *(7d)*, 66538-55-4; *(8a)* (E=D), 66538-56-5; *(8a)* (E=CH_3), 66538-57-6; *(8a)* (E=n-C_8H_{17}), 66538-58-7; *(8a)* (E=CH—$(CH_2)_4$), 66538-59-8; *(8a)* (E=CH_2—C_6H_5), 66538-60-1; *(8a)* [E=$(CH_3)_3CCH(OH)$] (isomer A), 66538-61-2; *(8a)* [E=$(CH_3)_3CCH(OH)$] (isomer B), 66538-62-3; *(8a)* [E=n-$C_5H_{11}CH(OH)$] (isomer A), 66538-63-4; *(8a)* [E=n-$C_5H_{11}C_4(OH)$] (isomer B), 66538-64-5; *(8a)* [E=$C_6H_5CH(OH)$] (isomer A), 66538-65-6; *(8a)* [E=$C_6H_5CH(OH)$] (isomer B), 66538-66-7; *(8a)* [E=$(CH_2)_5C(OH)$], 66538-67-8; *(8b)* (E=D), 66538-68-9; *(8b)* (E=CH_3), 66538-34-9; *(8b)* (E=n-C_8H_{17}), 66538-35-0; *(8b)* [E=$CH(CH_3)_2$], 66538-36-1; *(8b)* [E=$CH(CH_2)_4$], 66538-37-2; *(8b)* [E=$CH_2C_6H_5$], 66538-38-3; *(8b)* [E=$(CH_3)_3CCH(OH)$], 66538-39-4; *(8b)* [E=n-$C_5H_{11}CH(OH)$], 66538-40-7; *(8b)* [E=$C_6H_5CH(OH)$], 66538-41-8; *(8b)* [E=$(CH_2)_5C(OH)$], 66538-42-9; *(8b)* [E=$(C_6H_5)_2C(OH)$], 66538-43-0;
(8b) [E={—$(CH_2)_2$—CO—CH_2—}CH], 66538-44-1;
(8b) [E={—$(CH_2)_3$—CO—CH_2—}CH], 66538-45-2;
(8b) [E={—$(CH_2)_4$—CO—CH_2—}CH], 66538-46-3;
(8b) [E=$C_6H_5COCH_2CH(C_6H_5)$], 66538-47-4; *(9a)*, 36747-83-8; *(9b)*, 37868-70-5; *(10)*, 66538-48-5; D_2O, 7789-20-0; iodomethane, 74-88-4; 1-iodooctane, 629-27-6; 2-iodopropane, 75-30-9; bromocyclopentane, 137-43-9; benzyl bromide, 100-39-0; pivalaldehyde, 630-19-3; hexanal, 66-25-1; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; benzophenone, 119-61-9; 2-cyclopenten-1-one, 930-30-3; 2-cyclohexen-1-one, 930-68-7; 2-cycloheptenone, 1121-66-0; benzylideneacetophenone, 94-41-7; acetone, 67-64-1

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[2] *D. Seebach, F. Lehr*, Angew. Chem. *88*, 540 (1976); Angew. Chem. Int. Ed. Engl. *15*, 505 (1976); *R. Henning, F. Lehr, D. Seebach*, Helv. Chim. Acta *59*, 2213 (1976); *D. Seebach, R. Henning, F. Lehr, J. Gonnermann*, Tetrahedron Lett. *1977*, 1161.
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[4] *E. F. Witucki, G. L. Rowley, M. Warner, M. B. Frankel*, J. Org. Chem. *37*, 152 (1972).
[5] The adducts *(7c)* and *(7d)* with aromatic carbonyl compounds readily decompose to the starting materials on warming or storing in solution. Silylation of the alkoxides of the primary adducts with chloro(*tert*-butyl)-dimethylsilane affords the more stable silyl ethers, *e.g. (7b)*, $OSi(CH_3)_2(t$-$C_4H_9)$ in place of OH, n_D^{20}=1.4792.
[6] *J. E. McMurry, J. Melton*, J. Org. Chem. *38*, 4367 (1973); *T.-L. Ho, C. M. Wong*, Synthesis *1974*, 196.
[7] *(9a)*: 64%, DNP m.p. 146—147 °C [*C. Jutz*, Chem. Ber. *91*, 1867 (1958); m.p. 149—150 °C].—*(9b)*: 55%, DNP m.p. 168—169 °C.—*(10)*: 60%, ^{1}H-NMR: δ(CHO)=9.43 (d, 7.5 Hz), δ(Vinyl-H)=6.0 (dd, 15 and 7.5 Hz) and 6.71 (dt, 15 and 7.5 Hz).

Cathodic Acylation of Aryl Olefins[**]

By *Rainer Engels* and *Hans J. Schäfer*[*]

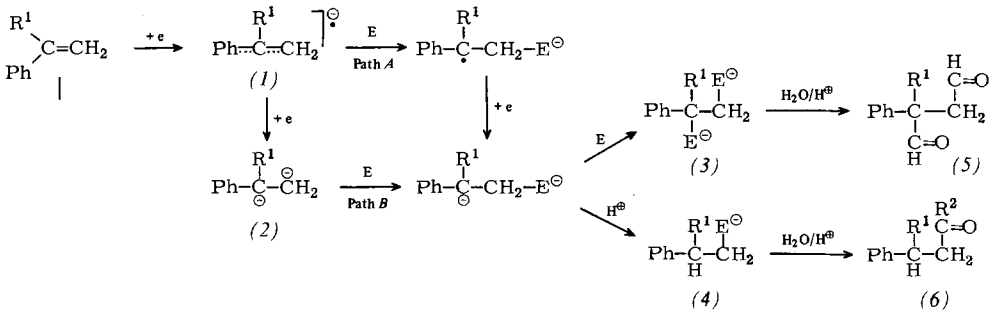
Electrochemical reductive acylation has so far only been accomplished with activated olefins such as α,β-unsaturated carboxylic esters and nitriles[1]. We have now found that aryl olefins can be cathodically acylated, and in particular formylated (see Table 1).

Table 1. Products and yields of reductive acylation of aryl olefins.

Aryl olefin [a]	Electrophile	Product (current efficiency)
α-Methylstyrene	Acetonitrile	4-Phenyl-2-pentanone (68 %) [b]
α-Methylstyrene	*n*-Butyronitrile	2-Phenyl-4-heptanone (50 %) [b, c]
α-Methylstyrene	*i*-Butyronitrile	2-Methyl-5-phenyl-3-hexanone (54 %) [b]
Styrene	Acetonitrile	4-Phenyl-2-butanone (20 %) [d]
		1,4-Diphenylbutane (48 %) [d]
α-Methylstyrene	*N,N*-Dimethylformamide	2-Methyl-2-phenylsuccinaldehyde (86 %) [d, e]
		(91 %) [d, e, h]
Styrene	*N,N*-Dimethylformamide	Phenylsuccinaldehyde (82 %) [d, f]
		2,5-Diphenyladipaldehyde (12 %) [d, f, g]

[a] Electrolysis conditions: 20 mmol of aryl olefin and 40 mmol of $LiClO_4$ in 80 ml of anhydrous electrophile, diaphragm cell, platinum mesh cathode, current density *ca.* 10 to 30 mA/cm², current passed 20 mF.
[b] Determined by gas chromatography (5 % SE 30 on Chromosorb W).
[c] 2-Methyl-2-phenyl-3-hexanone (3 %) was detected as by-product.
[d] Isolated yield.
[e] Isolated as 4-methyl-4-phenyl-4,5-dihydropyridazine.
[f] Isolated as *O*-methyloxime derivative.
[g] Small amounts of 2-phenylpropanal appear as a further minor product.
[h] Reduction by lithium in *N,N*-dimethylformamide.

The reduction of the aryl olefins $Ph(R^1)C{=}CH_2$ at the cathode (directly or by deposited lithium) leads to radical anions *(1)* and/or dianions *(2)*[2] which can react by path A or path B with the electrophilic solvent E.



R^1 = H, Me
E = HCO–NMe_2, R^2–C≡N; *(3)*: $E^{\ominus}$ = –CH–NMe_2, *(4)*: $E^{\ominus}$ = –C=$N^{\ominus}$
R^2 = Me, *n*Pr, *i*Pr

The resulting anionized hemi-aminals *(3)*[3] and ketimines *(4)*[4] are subsequently hydrolyzed to the products *(5)* and *(6)*, respectively.

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Procedure

α-Methylstyrene (2.36 g, 20 mmol) and lithium perchlorate (4.38 g, 40 mmol) are electrolyzed in anhydrous *N,N*-dimethylformamide (80 ml) at −10 °C in a diaphragm cell at a platinum mesh cathode (geometrical surface area 18 cm²) at a current density of *ca.* 25 mA/cm² until 20 mF have passed through the cell. The catholyte is added to a cold 80 % solution of hydrazine hydrate which has previously been acidified to pH 5 with conc. H_2SO_4, and the mixture is heated to 130 °C for 2 h. Bulb to bulb distillation (80—90 °C/0.1 torr) of the residue after the usual workup gives pure 4-methyl-4-phenyl-4,5-dihydropyridazine (1.48 g, 8.6 mmol) [^{1}H-NMR ($CDCl_3$): $\delta = 1.5$ (s, 3H), 4.5—4.65 (m, 1H), 6.2—6.4 (m, 2H), 7.1—7.4 (m, 6H); MS (70 eV): $m/e = 172$ (M^+, 4 %), 157 ($M^+ - CH_3$, 100 %)].

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CAS Registry numbers:
Products listed in Table 1 (top to bottom): 17913-10-9; 59540-81-7; 66515-35-3; 2550-26-7; 1083-56-3; 66515-34-2; 66515-33-1; 66515-32-0; α-methylstyrene, 98-83-9; styrene, 100-42-5; acetonitrile, 75-05-8; *n*-butyronitrile, 109-74-0; *i*-butyronitrile, 87-82-0; *N,N*-dimethylformamide, 68-12-2; 4-methyl-4-phenyl-4,5-dihydropyridazine, 66551-66-4; 2,5-diphenyladipinaldehyde *O*-methyl oxime, 66515-31-9

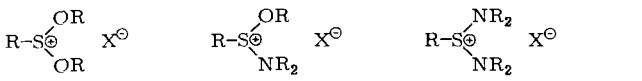
[1] *H. Lund, C. Degrand*, Tetrahedron Lett. *1977*, 3593; *T. Shono, I. Nishiguchi, H. Ohmizu*, J. Am. Chem. Soc. *99*, 7396 (1977).
[2] *G. J. Hoijtink, J. v. Schooten, E. de Boer, W. I. Aalbersberg*, Recl. Trav. Chim. Pays-Bas *73*, 355 (1954).
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[4] *P. L. Pickard, T. L. Tolbert*, J. Org. Chem. *26*, 4886 (1961).

Synthesis of Donor-substituted Sulfonium Salts

By *Hans-Ulrich Wagner* and *Aviv Judelbaum*[*]

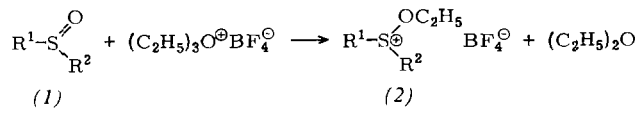
Despite their potential utility as synthetic intermediates, sulfonium salts of type *(A)* or *(B)* stabilized by donor substituents have hitherto not been isolated[1]. Only *N*-acyl derivatives of *(B)*[2] and a cyclic salt of type *(A)* stabilized with trifluoromethyl groups[3] have so far been described. *Kresze et al.* recently reported the synthesis of the related sulfonium salts *(C)*[4].

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(A) (B) (C) R = Alkyl, Aryl

We have now found that the sulfonium salts *(2)* are accessible in almost quantitative yields by alkylation of the sulfinic acid derivatives *(1)* with triethyloxonium tetrafluoroborate in dichloromethane[5]. Characteristic examples are listed in Table 1.

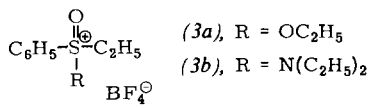


(1) *(2)*

Table 1. Some characteristic sulfonium salts *(2)*.

(2)	R^1	R^2	M.p. [°C]
(a)	C_6H_5	OC_2H_5	oil
(b)	C_6H_4-*p*-CH_3	OC_2H_5	28—30
(c)	C_6H_5	NH_2	oil
(d)	C_6H_5	NHC_2H_5	oil
(e)	C_6H_5	$NHCH(CH_3)_2$	oil
(f)	C_6H_5	$N(CH_3)_2$	18—19
(g)	C_6H_5	$N(C_2H_5)_2$	19—20
(h)	C_6H_5	$N[CH(CH_3)_2]_2$	139—141

The ^{1}H-NMR spectra of *(2a)* and *(2b)* show signals for *one* ABX_3 spin system for the protons of the ethyl groups[6] and thus afford evidence that the two ethoxy groups are equivalent, *i.e.* an alkylation of the sulfinate at the sulfur atom to give the salt *(3a)* can be ruled out. The given structure for the amino-substituted sulfonium salt *(2g)* could thus be demonstrated by the fact that the ^{1}H-NMR spectra of *(2g)*[7] and of the isomeric salt *(3b)* independently synthesized by us[8] are different.

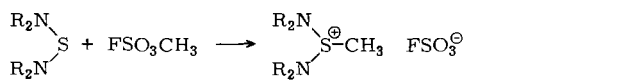


(3a), R = OC_2H_5
(3b), R = $N(C_2H_5)_2$

That the three ligands of the sulfur atom in the sulfonium salts *(2)* must also be oriented pyramidally, as in the sulfinic acid derivatives *(1)*, is revealed in the ^{1}H-NMR spectra of those salts which bear diastereotopic groups: the signals of the ethyl groups of *(2a)*, *(2b)*, and *(2d)* appear as an ABX_3 system with a relative chemical shift of the AB part of 0.02 to 0.04 ppm. Correspondingly, the signals of the isopropyl groups of *(2e)* and *(2h)* appear as an AX_3Y_3 system with the larger relative chemical shift of the X_3Y_3 part of 0.20 ppm. Only in the case of *(2g)*[7] is the relative chemical shift too small to be recognizable in the spectrum.

The colorless salts *(2)* are stable towards air and water. Towards nucleophiles such as sodium hydroxide, triethylamine, or aniline they act as alkylating agents leading to re-formation of the sulfinic acid derivatives. Results of preliminary experiments on the nucleophilic substitution of the ethoxy groups of *(2)* are encouraging.

Regarding the synthesis of sulfonium salts of type *(C)* we have found that the salt *(5)* is obtainable by alkylation of the sulfur diamide *(4)* with methyl fluorosulfonate.



(4) *(5)* R = $CH(CH_3)_2$

Alkylation of *(4)* at one of the two nitrogen atoms can be ruled out on the basis of the ^{1}H-NMR spectrum of *(5)*[9]. The appearance of only one heptet signal for the CH fragments and of two doublet signals for the diastereotopic CH_3 groups indicates alkylation of *(4)* at sulfur to give the symmetrical sulfonium ion *(5)*.

Procedure

To a solution of the sulfinic acid derivative *(1)* (15 mmol) in anhydrous CH_2Cl_2 cooled to −20 °C is added 10 mmol $Et_3O^{\oplus}BF_4^{\ominus}$. The mixture is allowed to stand for 3 d at −20 °C (+20 °C in the case of *(2a)* and *(2b)*) and then the solvent is removed by distillation *in vacuo*. The oily residue is washed several times with anhydrous ether. The solid sulfonium salts *(2)* (Table 1) crystallize out on storage of the residues in a refrigerator; they can be purified by pressing on a clay tile.

(5) is obtained by slow dropwise addition of 10 mmol *(4)* to 10 mmol FSO_3CH_3 at 0 °C. After 1 d at 0 °C the reaction mixture is dissolved in CH_2Cl_2 and treated with activated charcoal. The salt *(5)* is precipitated from the solution by addition of ether. Repetition of this purification three times affords *(5)* as a colorless powder (m.p. 196—198 °C) in *ca.* 70 % yield.

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[1] Review: *J. P. Marino* in *A. Senning:* Topics in Sulfur Chemistry, Vol. 1. Thieme, Stuttgart 1976.
[2] *M. Haake, H. Benack*, Synthesis *1976*, 308; and references cited therein.
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[5] The structure of the new salts was confirmed by elemental analysis and ^{1}H- and ^{13}C-NMR spectroscopy.
[6] ^{1}H-NMR data of *(2b)* in $CDCl_3$: $\delta = 7.83$ (4H) m, 2.57 (3H) s and an $(ABX_3)_2$ system with $\delta = 3.93$ ($2H_A$), 3.76 ($2H_B$), 1.63 ($6H_X$), $J_{AB} = -10$, $J_{AX} = J_{BX} = 7.3$ Hz.
[7] ^{1}H-NMR data of *(2g)* in $CDCl_3$: $\delta = 7.92$ (5H) m, 4.73 (2H) q, 3.50 (4H) q, 1.63 (3H) t, 1.35 (6H) t, $J = 7.4$ Hz.
[8] Synthesized by ethylation of phenyl(ethyl)sulfoximide with $Et_3O^{\oplus}BF_4^{\ominus}$ [cf. *C. R. Johnson, E. R. Janiga*, J. Am. Chem. Soc. *95*, 7692 (1973)]; ^{1}H-NMR data of *(3b)* in $CDCl_3$: $\delta = 8.01$ (5H) m, 4.38 (1H) q, 4.30 (1H) q, 3.60 (4H) q, 1.37 (9H) t, $J = 7$ Hz.
[9] ^{1}H-NMR data of *(5)* in $CDCl_3$: $\delta = 4.02$ (4H) h, 3.40 (3H) s, 1.43 (12H) d, 1.30 (12H) d, $J = 7$ Hz.

Cyclooctenynes[**]

By *Hermann Petersen, Heinz Kolshorn*, and *Herbert Meier*[*]

Linear arrangement of four carbon atoms on incorporation of a C≡C triple bond in a carbocyclic ring system is possible only from ten-membered rings onward. In smaller ring systems[1,2], such an arrangement leads to *geometrical ring strain*[1], defined as the sum of the individual deformation energies. Interaction between atoms not directly attached to each other induces additional deformations and hence also strain energies, which add to the sum total of *steric energy*.

The smallest stable cycloalkyne to have been isolated in pure form is cyclooctyne *(2)*[3]; ring strain and reactivity are enchanced when further sp^2 or sp carbon atoms are introduced into the eight-membered ring[4].

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Figure 1 shows the enthalpies of formation ΔH_f of cyclooctene *(1)*, cyclooctyne *(2)*, and the three *cis*-cyclooctenynes *(3)*—*(5)* obtained by semiempirical quantum mechanical calculations[5] with complete optimization of geometry in each case[6].

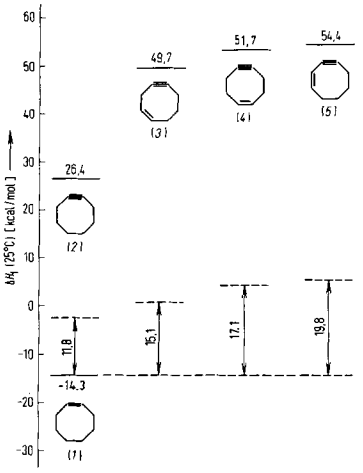
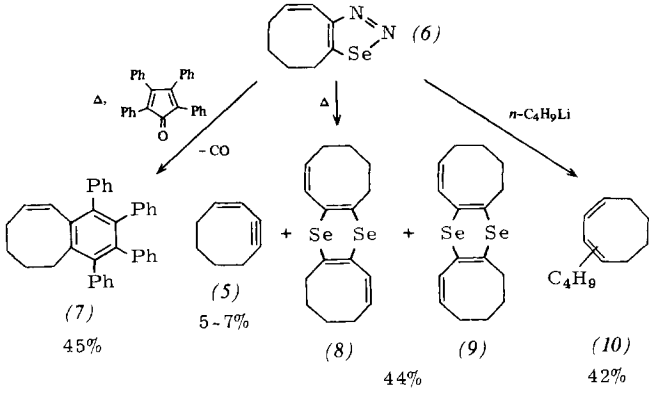


Fig. 1. Enthalpies of formation ΔH_f and strain energies E (dashed levels) of *(1)*—*(5)* calculated by the MINDO/2 procedure [5].

The ΔH_f values refer to the lowest energy conformations [symmetry (point group): *(1)*, *(3)*, *(5)* C_1; *(2)* C_2; *(4)* C_s]. Subtraction of the MINDO/2 value for the hydrogenation of an unstrained triple bond to a single bond (*e.g.* 2-butyne→*n*-butane) from the heats of formation of the enynes *(3)*—*(5)* and of the value for the hydrogenation to the *cis*-olefin (*e.g.* 2-butyne→*cis*-2-butene) from the enthalpy of formation of cyclooctyne *(2)* gives the excess enthalpies E (dashed lines). They constitute a direct measure of the ring strain. Since the non-bonding interactions in *(1)*—*(5)* are, to a first approximation, equal in magnitude, the values of E correspond to the geometrical strain. The value of 11.8 kcal/mol for cyclooctyne falls neatly in line with the values of 7—10 kcal/mol[7] determined experimentally from heats of hydrogenation and of 12.7[4] and 20.8 kcal/mol[8, 9] derived from force field calculations.

Compound *(5)*, with the conjugated system, is the most energy-rich of the *cis*-cyclooctenynes. Highly strained cycloalkynes can be readily prepared by fragmentation of the corresponding 1,2,3-selenadiazoles. We synthesized the selenadiazole *(6)* by reaction of the semicarbazone of *cis*-2-cyclooctenone with selenium dioxide (Method: [2d, 2f]). Thermolysis of *(6)* in xylene (130—140°C) leads to *(5)*, which was trapped *in situ* with tetraphenylcyclopentadienone (tetracyclone) as the bicyclic compound *(7)*.



Thermolysis (170°C) of neat *(6)* permitted isolation of *(5)*, which precipitates on the cold finger of the thermolysis apparatus at 70 torr. Column chromatographic separation of the residue afforded the 1,4-diselenins *(8)* and *(9)*. Fragmentation of *(6)* with *n*-butyllithium at −80°C also leads to *(5)*, which adds butyllithium and is subsequently converted on hydrolysis into *(10)*.—In similar experiments we have trapped *(3)* and *(4)* with tetracyclone.

Table 1. ^{13}C-NMR signals of cyclododecyne *(11)*, cyclooctyne *(2)*, *cis*-cyclododecen-3-yne *(12)*, and *cis*-cycloocten-3-yne *(5)* (δ values, $CDCl_3$, TMS internal).

	...—CH_2—	C≡≡C		—CH=CH—		Remaining
	α	sp	sp	sp^2	sp^2	C atoms
(11)	18.4	81.5		—		24.5, 24.9, 25.7, 26.3
(2)	20.8	94.4		—		29.7, 34.5
(12)	19.6	95.4	78.6	111.1	142.3	23.9, 25.1, 25.3, 26.4, 26.6, 26.8, 27.2
(5)	21.6	114.5	94.5	111.8	149.1	25.3, 32.9, 35.5

The highly reactive compound *(5)* is moderately stable at room temperature. Of the spectra recorded, we shall discuss here only the ^{13}C-NMR spectrum (Table 1). Comparison of the chemical shifts of cyclooctyne *(2)* and the unstrained cyclododecyne *(11)* shows that ring strain causes an overall downfield shift of the signals. Most pronounced is the effect on the signals of the sp carbon atoms ($\Delta\delta = 12.9$).

For comparison with *(5)*, we have prepared the unstrained *cis*-cyclododecen-3-yne *(12)* by thermolysis of the corresponding 1,2,3-selenadiazole. Ring strain causes a downfield shift of the signals also in the case of *(5)*, the sp carbon atoms once again being the most strongly affected ($\Delta\delta = 15.9$ and 19.1). The $\Delta\delta$ values can serve as a direct experimental measure of ring strain[2e].

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German version: Angew. Chem. 90, 483 (1978)

[1] *H. Meier*, Synthesis *1972*, 235.
[2] Examples: a) *H. N. C. Wong, P. J. Garatt, F. Sondheimer*, J. Am. Chem. Soc. *96*, 5604 (1974); b) *E. Kloster-Jensen, J. Wirz*, Helv. Chim. Acta *58*, 162 (1975); c) *A. Krebs, J. Odenthal, H. Kimling*, Tetrahedron Lett. *1975*, 4663; d) *H. Meier, M. Layer, W. Combrink, S. Schniepp*, Chem. Ber. *109*, 1650 (1976); e) *H. Meier, H. Gugel, H. Kolshorn*, Z. Naturforsch. *B31*, 1270 (1976); f) *H. Meier, H. Petersen*, Synthesis *1978*, in press.
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[4] *H. Meier*, Lecture at the Chemiedozententagung, Regensburg 1976.
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[8] *N. L. Allinger, A. Y. Meyer*, Tetrahedron *31*, 1807 (1975).
[9] The different definitions of strain energy should not be overlooked.

Unusual Reaction of Nickelocene with Bis(diphenylphosphino)maleic Anhydride

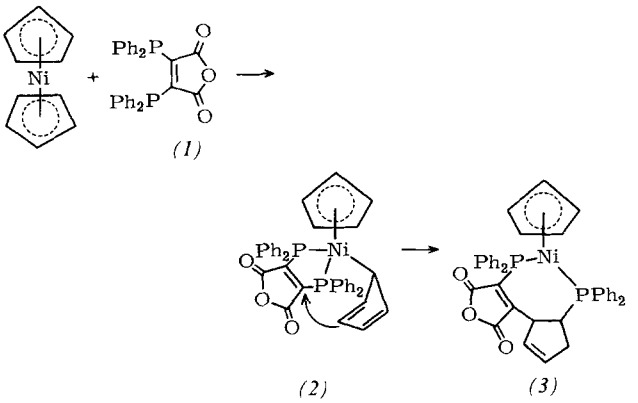
By *Walter Bensmann* and *Dieter Fenske*[*]

Nickelocene [bis(η^5-cyclopentadienyl)nickel, $NiCp_2$] reacts with potential mono- and bidentate phosphane ligands to form complexes obeying the noble gas rule. Organyl groups

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attached to the phosphorus can direct the reaction in various ways. Thus complexes of type $Ni(PR_3)_4$[1] are obtained with triphenylphosphane and tri-*n*-butylphosphane, and η^3-$CpNi(PPhBu_2)_2$[2] with di-*n*-butyl(phenyl)phosphane. With halonickel complexes of ethylenebis(diphenylphosphane) [diphos], $NiCp_2$ gives ionic compounds $[CpNi(diphos)]_2NiX_4$ (X = Cl, Br) or bridged complexes XCpNi(diphos)NiCpX (X = I, CN)[3].

We have now discovered a novel insertion of the C_5H_5 ligand into a P—C bond of the bisphosphane ligand on reaction of $NiCp_2$ with bis(diphenylphosphino)maleic anhydride *(1)*[4]:



The high yield (70%) of *(3)* suggests that the insertion reaction takes place within the coordination sphere of nickel. ESR measurements indicate formation, immediately upon addition of *(1)* to $NiCp_2$, of a triplet radical—presumably *(2)*—which is no longer detectable after 24 h. During this time the color of the solution changes from red to green and crystals of the diamagnetic compound *(3)* are precipitated.

X-Ray structure analysis of a single crystal of *(3)* showed a 1:1 adduct with benzene to be present: space group $P2_1/c$, $a = 1294.7(6)$, $b = 1983.9(16)$, $c = 1474.1(12)$ pm, $\beta = 94.42(3)°$, $d_{exp} = 1.28$, $d_{calc} = 1.31\ g\,cm^{-3}$, $Z = 4$, $\mu(Mo_{K\alpha}) = 6.4\ cm^{-1}$. Data collection: Syntex $P2_1$ diffractometer up to $2\theta = 40°$, 3539 reflections of which 2160 had $I > 1.96\sigma(I)$. Solution: heavy atom method, isotropic refinement of all positional parameters and isotropic temperature factors; $R_1 = 0.082$, $R_2 = 0.081$. Hydrogens could not be localized. As shown by Figure 1, a cyclopentadienyl group has inserted into one of the P—C bonds of the coordinated bisphosphane *(1)*. This ring then only has one double bond between C8 and C9; C6 and C7 are sp^3 hybridized. The C5 and C2 atoms are each surrounded by a planar arrangement of three carbon atoms; therefore they cannot bear any hydrogen atoms. The C5—C2 distance suggests a strengthening of the bond. The C2—C3 double bond of the anhydride ring is unusually long (145(2) pm). This ring becomes unsymmetrical as a result of C_5H_5 insertion (cf. Fig. 1).

The two C=O bond lengths (120 and 121 pm) are also lengthened relative to the values for diamagnetic metal complexes of *(1)*[4]; a similar lengthening was also observed in the paramagnetic complex *(1)*·$Co(CO)_3$[5]. The special bonding situation is even more apparent from a pronounced drop in the ν(C=O) frequency of *(3)* as compared with that for free *(1)* or its complexes with normal electron configuration[4, 5]. We attribute it to an electronic transition from nickel into a low-lying π^*MO of the ligand *(1)*.

The Ni—Cp distances of 210—216(2) pm lie in the same range as for other η^5-cyclopentadienyl complexes[6].

If the nickel of $NiCp_2$ is assigned the oxidation number zero, then a C_5H_5 group with an unpaired electron is inserted into the ligand *(1)* on formation of *(3)*. The resulting bisphosphane ligand of *(3)* should also contain a single electron. On the other hand, this ligand (as a donor of two electron pairs) and the remaining Cp ligand (as a five-electron donor) formally lead to the presence of 37 electrons on the Ni. As in the case of the complex *(1)*·$Co(CO)_3$ with a similar electron complement, one electron is apparently transferred from the metal into an antibonding πMO of the phosphane-substituted anhydride group [ν(C=O) in *(3)*: 1748 and 1692 cm^{-1}], which extends into the inserted cyclopentadienyl ring, leading to spin pairing with the single electron initially formally present there.

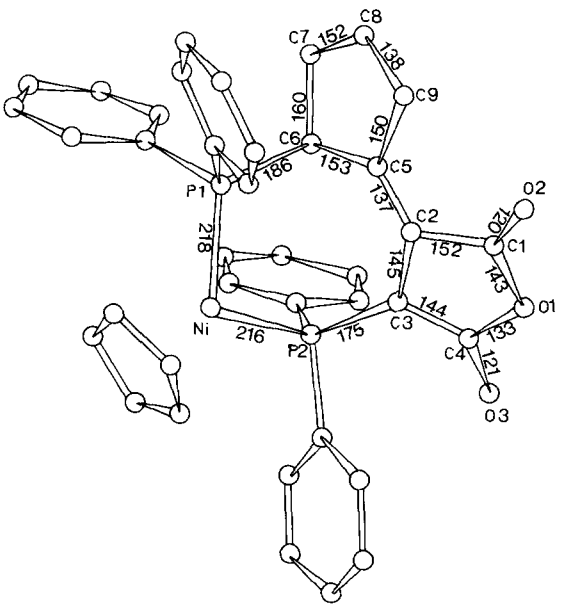


Fig. 1. Molecular structure of the complex *(2)* in its crystal (atomic distances in pm).

Experimental

(1) (1.0 g, 2.14 mmol) in benzene (60 ml) is added dropwise to nickelocene (0.38 g, 2.01 mmol) in benzene (30 ml). Cyclohexane is added after 24 h. Compound *(2)* is precipitated as green crystals within a few days.

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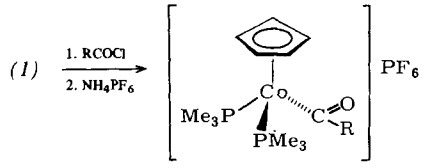
CAS Registry numbers:
(1), 51501-24-7; *(2)*, 66652-76-4; *(3)*, 66687-76-1; $NiCp_2$, 1271-28-9

[1] *G. R. von Hecke, W. D. Horrocks*, Inorg. Chem. 5, 1968 (1966); *H. Behrens, K. Meyer*, Z. Naturforsch. *B 21*, 489 (1966); *H. Werner, V. Harder, E. Deckelmann*, Helv. Chim. Acta *52*, 108 (1969); *E. Uhlig, H. Walther*, Z. Chem. *11*, 23 (1971).
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[3] *L. A. Kaempfe, K. W. Barnett*, Inorg. Chem. *12*, 2578 (1973).
[4] Cf. *H. F. Becher, W. Bensmann, D. Fenske*, Chem. Ber. *110*, 315 (1977); *D. Fenske, ibid.*, in press; references cited therein.
[5] *D. Fenske*, Angew. Chem. *88*, 415 (1976); Angew. Chem. Int. Ed. Engl. *15*, 381 (1976).
[6] *L. Hedberg, K. Hedberg*, J. Chem. Phys. *53*, 1228 (1970); *K. W. Barnett*, J. Organomet. Chem. *78*, 139 (1974).

Reductive Elimination Reactions of Cationic Acylcobalt Complexes: Transformation of a Co^{III}—COR Bond into a Co^{I}—CO Bond[1]

By *Helmut Werner* and *Werner Hofmann*[*]

The cobalt compound $C_5H_5Co(PMe_3)_2$ *(1)*, which possesses a strongly nucleophilic metal atom and forms the hydrido complex $[C_5H_5(PMe_3)_2CoH]^+$ with weak protic acids such as H_2O or MeOH[2], reacts with acyl chlorides to give the cations $[C_5H_5(PMe_3)_2Co(COR)]^+$ which can be isolated as the hexafluorophosphates.



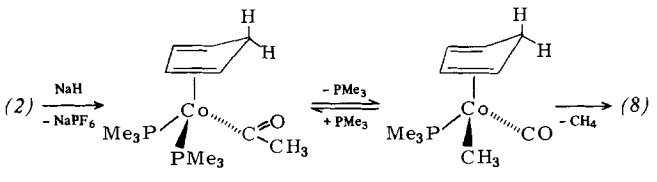
(2), R = CH_3
(3), R = C_6H_5
(4), R = p-$C_6H_4OCH_3$
(5), R = p-$C_6H_4CH_3$
(6), R = m-$C_6H_4CH_3$
(7), R = 3,5-$C_6H_3(OCH_3)_2$

The yellow, air-stable salts *(2)*—*(7)*, which were characterized by elemental analysis and IR and NMR spectra, are completely inert towards strong acids such as CF_3COOH. This suggests that, in contrast to comparable acylmetal complexes such as acylmetal carbonyls assumed to have a charge distribution $M^{\delta+}$—$COR^{\delta-}$, the cations $[C_5H_5(PMe_3)_2Co(COR)]^+$ contain an acyl group exhibiting umpolung[3].

This is supported by the reactions of *(2)*—*(7)* with strong bases and nucleophiles, the product patterns being highly dependent upon the group R in the acyl moiety. Reaction of *(2)* and NaH in tetrahydrofuran affords *quantitatively* the neutral carbonyl complex *(8)*; moreover, one equivalent each of methane and PMe_3 are formed.

$$(2) + NaH \xrightarrow{THF} \underset{(8)}{C_5H_5Co(CO)PMe_3} + CH_4 + PMe_3$$

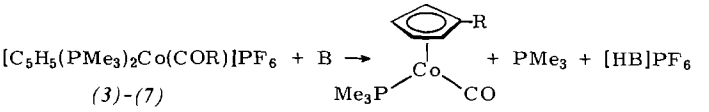
We assume the mechanism of this novel *reductive elimination* to involve initial attack on the cyclopentadienyl ring by the hydride ion to give the intermediate *(A)*. Dissociation of a Co—PMe_3 bond in this species and concomitant migration of CH_3 to the metal gives the carbonylmethyl complex *(B)*, which undergoes loss of methane to form the dicarbonyl(cyclopentadienyl)cobalt derivative *(8)*. Reaction of *(2)* and phenyllithium in ether consequently gives $C_5H_4PhCo(CO)PMe_3$.



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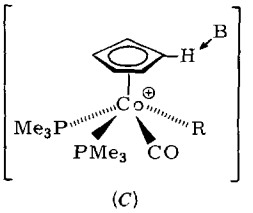
The reversibility of the process *(A)*⇌*(B)* + PMe_3 confirms the result of the reaction of *(2)* with NaH in the presence of PEt_3 which gives not only *(8)* but also the corresponding triethylphosphane compound $C_5H_5Co(CO)PEt_3$ *(9)*.

The cations of the salts *(3)*—*(7)* with R = *aryl* react with NaH in THF basically in the same way as $[C_5H_5(PMe_3)_2Co(COMe)]^+$. Elimination of ArH and PMe_3 again gives *(8)*. In addition, the ring-substituted complexes *(10)*—*(14)* are also formed. We attribute this to the inevitable presence of base in the reaction system on use of commercial NaH in THF—the strong base B effects the side reaction mentioned. Reaction of the salts *(3)*—*(7)*, with for example DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) in THF or acetone yields quantitatively the monocarbonyl complexes *(10)*—*(14)*.



(10), R = C_6H_5
(11), R = p-$C_6H_4OCH_3$
(12), R = p-$C_6H_4CH_3$
(13), R = m-$C_6H_4CH_3$
(14), R = 3,5-$C_6H_3(OCH_3)_2$

We rationalize the mechanism of this ring substitution, which likewise involves *reductive elimination*, as proceeding *via* initial interaction of base B with a proton of the ring to give an "acid-base adduct" from which a transition state (or labile intermediate) of composition *(C)* is formed, possibly with an η^3-cyclopentadienyl ligand. Subsequent fast migration of the aryl group R to the ring and elimination of HB^+ (and of PMe_3) leads to the reaction product. We recently described a similarly facile ring substitution, *i.e.* that of *(1)* to give $C_5H_4RCo(PMe_3)_2$ (R = *i*Pr, *t*Bu, $SiMe_3$, *etc.*)[4].



(C)

Reaction of the *acetyl* complex *(2)* with NaOH in THF at 25 °C gives the methyl compound $[C_5H_5(PMe_3)_2CoMe]PF_6$ *(15)*. The corresponding iodide is readily prepared by direct reaction of *(1)* with MeI[2]. *In the absence of base*, no elimination of CO takes place from the cation $[C_5H_5(PMe_3)_2Co(COMe)]^+$ even at elevated temperature. It therefore appears plausible that the formation of $[C_5H_5(PMe_3)_2CoMe]^+$ from $[C_5H_5(PMe_3)_2Co(COMe)]^+$ and OH^- proceeds *via* a transition state similar to *(C)*.

So far, we have observed initial attack at the *metal* or the *acyl carbonyl atom* only on reaction of *(2)* with methyllithium in ether. The sole products are *(1)* and acetone; no formation of *(8)* or *(15)* was detected.

$$(2) + MeLi \xrightarrow{Et_2O} (1) + Me_2CO + LiPF_6$$

Experimental

The salts *(2)*—*(7)* are stirred with an excess of NaH in THF for *ca.* 4 h at 50 °C. After removal of solvent, the residue

is extracted into pentane, and the compounds *(8)* and *(10)*—*(14)* are precipitated by cooling of the pentane solution to −78 °C. Yield almost quantitative.

The reaction of *(3)*—*(7)* with an excess of DBU in acetone at 50 °C requires *ca.* 1 h. The red-brown solution is allowed to react with NH_4PF_6 to remove the excess of base and the solvent then removed. The oily residue is extracted with ether and the corresponding products *(10)*—*(14)* isolated by precipitation from ether/pentane at −78 °C.

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CAS Registry numbers:
(1), 63413-01-4; *(2)*, 65588-94-5; *(3)*, 65588-96-7; *(4)*, 66652-75-3; *(5)*, 66652-92-4; *(6)*, 66652-90-2; *(7)*, 66652-88-8; *(8)*, 66652-86-6; *(9)*, 66652-85-5; *(10)*, 66652-84-4; *(11)*, 66687-73-8; *(12)*, 66652-83-3; *(13)*, 66652-82-2; *(14)*, 66652-81-1; CH_3COCl, 75-36-5; C_6H_5COCl, 98-88-4; $CH_3OC_6H_4$-*p*-COCl, 100-07-2; $CH_3C_6H_4$-*p*-COCl, 874-60-2; $CH_3C_6H_4$-*m*-COCl, 1711-06-4; 3,5-$(CH_3O)_2C_6H_3COCl$, 17213-57-9

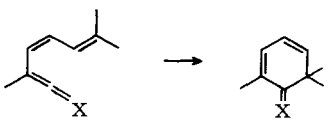
[1] Basic Metals, Part 8. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Bayer AG, Leverkusen. Part 7: *H. Werner, W. Bertleff*, J. Chem. Res., in press.
[2] *H. Werner, W. Hofmann*, Chem. Ber. *110*, 3481 (1977).
[3] *D. Seebach*, Angew. Chem. *87*, 1 (1975); Angew. Chem. Int. Ed. Engl. *14*, 1 (1975).
[4] *H. Werner, W. Hofmann*, Angew. Chem. *89*, 835 (1977); Angew. Chem. Int. Ed. Engl. *16*, 794 (1977).

Dienylketenimines—An Entry to Linearly Conjugated Cyclohexadienimines

By *Heinz H. Eckhardt* and *Hartwig Perst*[*]

Whereas the chemistry of linearly conjugated cyclohexadienones has been thoroughly investigated[1], the properties of the analogous cyclohexadienimines have remained essentially unknown. This is probably due mainly to the lack of a general method for their synthesis; presumably this is also the reason why no *N*-alkyl and *N*-aryl derivatives have previously been described[2]. We have now discovered a novel entry to this series.

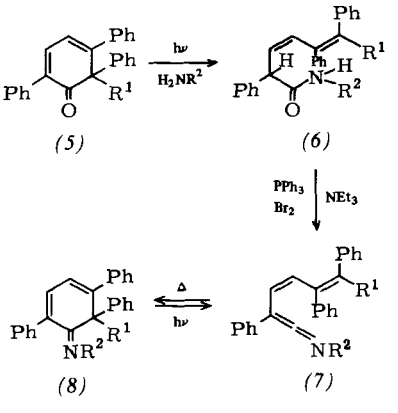
Just as dienylketenes *(1)* are able to give linearly conjugated cyclohexadienones *(2)*[3,4], dienylketenimines *(3)* should be capable of forming cyclohexadienimines *(4)*.



(1), (3) *(2), (4)*

(1), (2): X = O
(3), (4): X = NR

We first accomplished a reaction of this kind in the case of triarylated dienylketenimines *(7)*. In contrast to the frequently demonstrated dienylketene intermediates[3,4], the dienylketenimines *(7)* were previously unknown. *N*-Monosubstituted hexadienamides *(6)* represent potential precursors. These compounds are themselves readily accessible as trapping products of dienylketenes of type *(1)* *via* photochemically induced *cyclo/seco* isomerization of linearly conjugated cyclohexadienones *(5)* in the presence of primary amines[3-5]. Subsequent dehydration occurs smoothly with triphenylphosphane, bromine, and triethylamine in boiling dichloromethane[6]. While diarylketenimines are stable under these conditions[6], the expected dienylketenimines *(7)* cannot be isolated. Dehydration of *(6)* affords the cyclization products of *(7)*; we obtained the *N*-alkylated cyclohexadienimines *(8a)*—*(8e)*[7] in up to 80 % yield as colorless to pale yellow compounds[9].



(5) *(6)* *(8)* *(7)*

(5a), $R^1 = CH_3$
(5b), $R^1 = OCH_3$[8]
(5c), $R^1 = OCO{-}CH_3$[4]

(6)-*(8)*	R^1	R^2
(a)	CH_3	i-C_3H_7
(b)	CH_3	CH_3
(c)	OCH_3	i-C_3H_7
(d)	OCH_3	CH_3
(e)	$OCO{-}CH_3$	CH_3

The cyclohexadienimines *(8)* themselves provide an entry to dienylketenimines *(7)*. Thus, *(7a)* can be generated by UV irradiation of a solution of *(8a)* and can be detected together with unreacted *(8a)* in the IR [$\tilde{\nu} = 2000\,cm^{-1}$[6]; in 2-methyltetrahydrofuran (MTHF)] and in the ^{1}H-NMR spectrum [$\delta(CH_3) = 2.02$ (R^1), 1.26, $J = 7$ Hz (R^2), in [D_8]tetrahydrofuran ([D_8]THF)]. The lifetime of the dienylketenimine *(7a)* is highly solvent dependent: it is stable for several days in MTHF or [D_8]THF at room temperature; although also stable in [D_8]toluene at −60 °C, it regenerates *(8a)* within a few minutes above 0 °C.

Experimental

Synthesis of *(8a)*: A solution of isopropylamine (50 ml, 3 M in benzene) is added to a solution of compound *(5a)*[10] (2.0 g) dissolved in benzene (400 ml) and the mixture is irradiated (Hanau TQ 150 high pressure Hg lamp; photoreactor, Normag-Hofheim, Germany) at room temperature under nitrogen until decoloration is complete (*ca.* 22 min). After removal of solvent, *(6a)* can be crystallized with *n*-hexane and recrystallized from ethanol/*n*-hexane; yield 2.25 g (96 %) of *(6a)*, m.p. 88—90 °C.—A solution of bromine (1.8 g, 11 mmol) in dichloromethane (10 ml) is added under nitrogen to a solution of triphenylphosphane (2.9 g, 11 mmol) in anhydrous dichloromethane (40 ml), followed by addition of triethylamine (9 ml). To the resulting solution is added *(6a)* (2.25 g, 6 mmol). After heating (5 h under reflux) and removal of solvent, the residue is taken up in benzene (50 ml), filtered and dried over Na_2SO_4. The solution is concentrated, chromatographed over silica gel (activity II), eluted with benzene, evaporated down *in vacuo*, and *(6a)* (0.5—0.6 g, 22—27 %) is precipitated with *n*-hexane. The mother liquor is concentrated, the pale yellow oil made to crystallize with a small volume of methanol, and once again allowed to dissolve and precipitate from chloroform/methanol: the procedure affords (1.0—1.3 g of colorless *(8a)* 70—80 % based on reacted *(6a)*. M.p. 115 °C; MS: $m/e = 377$ (M^+, 92 %), 334 ($M^+ - C_3H_7$, 100 %); ^{1}H-NMR (C_6D_6): $\delta = 1.04$ (d, 6 H, $J = 7$ Hz, isopropyl-CH_3),

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2.05 (s, 3H, CH_3), 3.69 (hept., 1H, $J=7$ Hz, tert. H), 6.15 and 6.28 (AB, 2H, $J=6$ Hz, vinyl-H), 6.75–7.80 (m, 15H, phenyl-H); ^{13}C-NMR ($CDCl_3$): $\delta=164.9$ (C=N), 51.0 (N—CH), 24.2 and 22.4 (isopropyl-CH_3); UV (cyclohexane): $\lambda_{max}=337$ (4.20), 250 (4.00) sh, $\lambda_{min}=283$ (3.63); IR (KBr): $\nu_{C=N}=1630\,cm^{-1}$ (m). The preparation and spectroscopic data of *(8b)*—*(8e)* closely resemble those given for *(8a)*.

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[1] Survey: *A. J. Waring*, Adv. Alicycl. Chem. *1*, 129 (1966); references cited therein.
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[7] The configuration at the C=N bond has not yet been established: only one stereoisomer is observed for *(8a)* and *(8b)* whereas two stereoisomers can be detected for *(8c)* and *(8d)*.
[8] *H. Perst*, Tetrahedron Lett. *1970*, 4189.
[9] Attempted conversion of *(5)* into *(8)* led to dienone-phenol rearrangement (cf. [1]).
[10] *H. H. Eckhardt, H. Perst*, to be published.

Novel Coordination of (Benzoylmethylene)triphenylphosphorane in a Nickel Oligomerization Catalyst[**]

By *Wilhelm Keim, Frank H. Kowaldt, Richard Goddard*, and *Carl Krüger*[*]

The oligomerization of ethylene to linear α-olefins is of substantial technical interest[1]. On reacting $Ph_3P{=}CH{-}CO{-}Ph$ with $Ni(PPh_3)_4$ or $Ni(cod)_2/Ph_3P$ [cod = 1,5-cyclooctadiene] in toluene we obtained a compound of the composition $C_{44}H_{36}OP_2Ni$ *(1)*, the first well defined and readily crystallizable complex, which converts ethylene in high selectivity and activity into α-olefins or also polyethylenes in the absence of cocatalysts such as are required *e.g.* by catalysts of the Ziegler type.

The structure of the complex *(1)* followed from spectroscopic data (^{1}H- and ^{13}C-NMR, IR, MS) and from a crystal structure analysis[2] (cf. Fig. 1). The nickel atom is surrounded in an almost square planar arrangement by a triphenyl moiety, a σ-bonded phenyl group and a bidentate ylide ligand bonded *via* O and P (deviations from planarity of $+0.07\,m^{-10}$ for C1, O; $-0.07\,m^{-10}$ for P1, P2). The bond lengths and angles in the planar PC_2ONi five-membered ring indicate a delocalized system with typical P—C and P—Ni bond lengths[3]. As in the triphenylphosphane coordinated *via* P2 to Ni, both the phenyl groups attached to P1 are oriented in a propeller-like arrangement. The Ni—Cl σ-bond is unusually short ($1.893\,m^{-10}$); in comparable Ni—Ph compounds[4] values of 1.96—$2.00\,m^{-10}$ are observed. This finding might be explained in terms of a strong electron affinity of the *O,P*-ligand. ESCA analyses confirm this assumption.

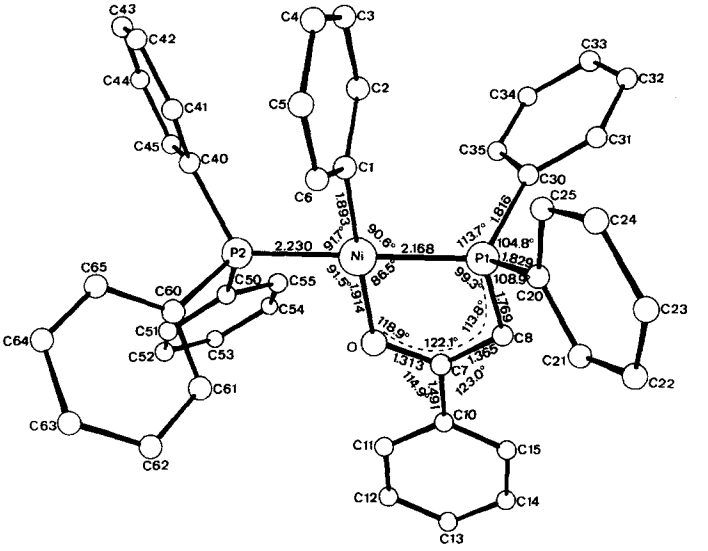
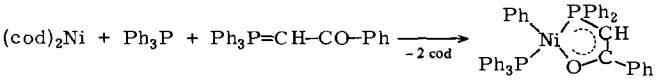


Fig. 1. Molecular structure of the complex *(1)* in the crystal.

The formation of *(1)* according to



(1)

proceeds *via* a novel type of phenyl rearrangement leading to a phenyl-metal bond. A 1,2-migration of a phenyl group in phosphorus ylides catalyzed by nickel compounds is already known[5].

Reaction of a toluene solution of the complex *(1)* with ethylene (50 bar) at 50 °C affords *n*-olefins which are up to 99 % linear and consist of up to 98 % of α-olefins. The olefins up to C_{30} analyzed by gas chromatography are present in a geometrical distribution. Activities of 6000 mol ethylene per mol of complex *(1)* are achieved. When the reaction of *(1)* with ethylene is carried out in *n*-hexane as suspension medium, however, high molecular linear polyethylene is formed.

Procedure

A solution of triphenylphosphane (26.2 g, 0.1 mol) and (benzoylmethylene)triphenylphosphane[6] (38 g, 0.1 mol) in toluene (900 ml) is added dropwise to a solution of bis(cyclooctadiene)nickel(0) (27.5 g, 0.1 mol) in toluene (600 ml) at 0 °C and the mixture stirred for 24 h at room temperature and a further 2 h at 50 °C. It is then evaporated to dryness in a vacuum at 50 °C. The toluene distilled over contains almost quantitatively the liberated 1,5-cyclooctadiene. The brownish-red crude reaction product is dissolved in toluene at 50—70 °C and treated with a small amount of *n*-octane. On cooling to 0 °C, 48.5 g (69 %) of compound *(1)* crystallizes out.

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

CAS Registry numbers:
(1), 66674-76-8; $(Cod)_2Ni$, 1295-35-8; Ph_3P, 603-35-0; $Ph_3P{=}CH{-}CO{-}Ph$, 859-65-4

[1] *W. Keim, R. S. Bauer, H. C. Chung, P. Glockner*, US-Pat. 3635937 (1969); *W. Keim, R. F. Mason, P. Glockner*, US-Pat. 3647914 (1972); DOS 2054009 (1972); Eur. Chem. News, Sept. 16, 60 (1977).

[2] Cell data: $a = 14.4341(6)$, $b = 16.2935$, $c = 9.6575(6)$ m^{-10}, $\alpha = 103.897(2)$, $\beta = 97.636(2)$, $\gamma = 80.177(3)°$, $V = 2162.4\ m^{-30}$, space group $P\bar{1}$, $Z = 2$, with a toluene molecule at $\bar{1}$, $d_c = 1.257\ g\,cm^{-3}$. 9123 reflections ($\lambda = 1.5418$ m^{-10}), 1646 unobserved (2σ); $R = 0.067$, $R_w = 0.099$.

[3] *B. L. Barnett, C. Krüger, J. Cryst. Mol. Struct. 2, 271 (1972); D. J. Brauer, C. Krüger, P. J. Roberts, Y.-H. Tsay*, Chem. Ber. *107*, 3706 (1974).

[4] *C. Krüger, Y.-H. Tsay*, Angew. Chem. *85*, 1051 (1973); Angew. Chem. Int. Ed. Engl. *12*, 998 (1973); *D. J. Brauer, C. Krüger, P. J. Roberts, Y.-H. Tsay, ibid. 88*, 52 (1976) and *15*, 48 (1976), respectively; *K. Jonas, D. J. Brauer, C. Krüger, P. J. Roberts, Y.-H. Tsay*, J. Am. Chem. Soc. *98*, 74 (1976).

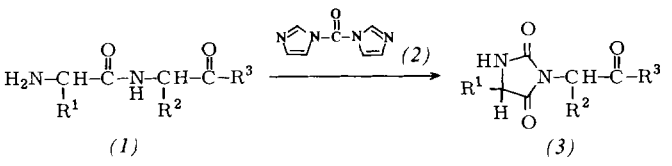
[5] *F. Heydenreich, A. Mollbach, G. Wilke, H. Dreeskamp, E. G. Hoffmann, G. Schroth, K. Seevogel, W. Stempfle*, Isr. J. Chem. *10*, 293 (1972).

[6] *F. Ramirez, S. Dershowitz*, J. Org. Chem. *22*, 43 (1957).

N-Terminal Cyclization of Peptides with *N,N'*-Carbonyldiimidazole or *N,N'*-Thiocarbonyldiimidazole

By *Franz Esser* and *Otto Roos*[*]

We have found that *N,N'*-carbonyldiimidazole *(2)*[1] reacts smoothly and without racemization under very mild conditions with C-terminally protected peptides to give hydantoin peptides of type *(3)* [*(3c)* and *(3d)* after removal of the benzyl protecting group]. This cyclization can also be carried out on a solid phase[2].

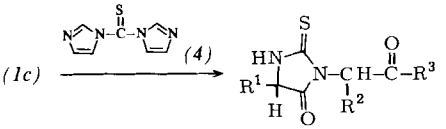


(1) *(3)*

	R^1	R^2	R^3
(3a)	*(S)*-$CH_2CO_2CH_2Ph$	*(S)*-CH_2Ph	NH_2
(3b)	H	*(S)*-3-Indolylmethyl	Met-Gly-NH_2
(3c)	*(S)*-3-Indolylmethyl	*(S)*-CH_2—$CH(CH_3)_2$	Asp-Phe-NH_2
(3d)	*(R)*-3-Indolylmethyl	*(S)*-CH_2—$CH(CH_3)_2$	Asp-Phe-NH_2

The significance of the procedure lies in the fact that it provides a convenient entry to such modified peptides which are of interest for the study of structure activity-relations of peptide hormones. Previous methods[3] required relatively drastic conditions and their scope is therefore very limited.

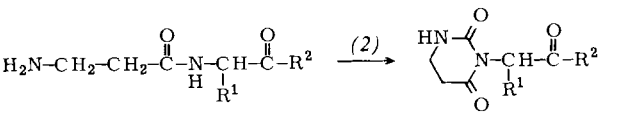
By analogy with the hydantoins *(3)*, thiohydantoins *(5)* are obtained by reaction with *N,N'*-thiocarbonyldiimidazole *(4)*.



(1c) *(4)* *(5)*

R^1 = *(S)*-3-Indolylmethyl, R^2 = *(S)*-CH_2-$CH(CH_3)_2$
R^3 = Asp(CH_2Ph)-Phe-NH_2

Peptides *(6)* containing an N-terminal β-amino acid cyclize with *(2)* to form 2,4-pyrimidinediones *(7)*.



(6) *(7)*

R^1 = *(S)*-CH_2Ph, $R^2 = NH_2$

Characteristic data for six selected products are compiled in Table 1. Ring formation is readily seen in the ^{13}C-NMR spectra. The expected signals (Table 1)[4] are accompanied by a typical shift of the C_α signals of the second amino acid unit relative to the corresponding signals of the open-chain compounds. Diastereomers such as *(3c)* and *(3d)* can be unequivocally distinguished. The expected molecular ions were observed in the mass spectra of *(3a)* and *(7)*, and the species *(8)* containing the hydantoin ring could be detected as key fragment in the case of *(3b)*[5].

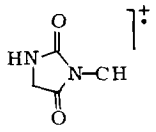
That the compounds synthesized were indeed N-terminally cyclized structures and not ureas of type *(9)* was proved as follows: For example amino acid analysis of *(3c)* revealed a Trp:Leu:Asp:Phe ratio of 0.27:0.46:1.01:1.0 on acidic degradation[6] and a ratio of 0.99:0.95:0.97:1.0 on alkaline hydrolysis[7]. The incomplete regeneration of the first two amino acids on acid hydrolysis can only be rationalized by

Table 1. Selected data of compounds produced.

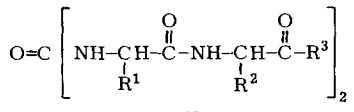
	Reactant	Product	Method	Yield [%]	M.p. [°C] (dec.)	R_f [d]	$[\alpha]_D^{20}$ (*c* = 1, DMF)	^{13}C-NMR [e]
(1a)	H-Asp(CH_2Ph)-Phe-NH_2	*(3a)*	A	88	166—169	0.96	−131.8	155.6
(1b)	H-Gly-Trp-Met-Gly-Pol [f]	*(3b)*	B	40 [a]	136	0.24	− 18.61	157.7
(1c)	H-Trp-Leu-Asp(CH_2Ph)-Phe-NH_2	*(3c)*	A	60 [b]	161—162	0.2	—	155.8
(1c')	H-Trp-Leu-Asp(CH_2Ph)-Phe-BzPol [g]	*(3c)*	B	94 [c]	158—160	0.2	− 44.7	—
(1d)	H-D-Trp-Leu-Asp(CH_2Ph)-Phe-BzPol [g]	*(3d)*	B	74 [c]	152—154	0.23	− 18.60	158.9
(1c)	H-Trp-Leu-Asp(CH_2Ph)-Phe-NH_2	*(5)*	A	91	103—115	0.83	− 27.34	184.3
(6)	H-β-Ala-Phe-NH_2	*(7)*	A	77	133—135	0.6	− 6.54	148.4

[a] Based on amino acid linked to the Merrifield resin; after ammonolytic cleavage. [b] After hydrogenolytic debenzylation. [c] Based on amino acid linked to benzhydrylamine resin; after acidolytic cleavage. [d] Eluent: $CHCl_3$:MeOH:H_2O = 65:25:4. [e] Signal of the C-atom of the newly introduced CO or CS group (TMS = 0, in [D_6]DMSO); Dr. *K. H. Pook*, Ingelheim. [f] Pol = Merrifield resin. [g] BzPol = benzhydrylamine resin.

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(8)



(9)

assuming their participation in a hydantoin ring which is completely degraded only in an alkaline medium. Conversely, this method is suitable for identification of the first two amino acids of a peptide of unknown sequence, resembling the method tried by *Wessely*[3d].

Experimental

(3c) by classical method (A): A solution of H-Trp-Leu-Asp(CH_2Ph)-Phe-NH_2·HCl (2 g, 2.9 mmol) in anhydrous dimethylformamide (DMF) (50 ml) was neutralized with triethylamine and added dropwise over 30 min at room temperature to a solution of *(2)* (0.55 g, 3.6 mmol) in DMF (50 ml) with exclusion of moisture. The mixture was left to stand overnight, stirred into an approximately tenfold volume of water, and the white precipitate was isolated. After dissolution in methanol, precipitation by dropwise addition to water, and drying, the hydantoin peptide benzyl ester was obtained (1.9 g, 94 %). A solution of this ester in glacial acetic acid was treated with H_2 in the presence of Pd/C as catalyst; yield 1.05 g (64 %) of *(3c)*.

(3c) by the solid phase method (B): Boc-Phe-OH, Boc-Asp(CH_2Ph)—OH, Boc-Leu-OH, and Boc-Trp-OH were successively linked by standard procedures[2] to 15 g of a 2% divinylbenzene-crosslinked benzhydrylamine-polystyrene resin (Pierce, USA). The resin was then treated for 2 h with a solution of *(2)* (13 g, 80 mmol ≙ 16 equiv. based on Boc-Phe loaded resin) in DMF (150 ml) at room temperature. The hydantoin peptide was subsequently cleaved from the dried resin by liquid HF in the presence of 10 % of anisole (1 h at 0 °C)[2]. After removal of HF and anisole the product was extracted with glacial acetic acid, the solvent removed, the residue taken up in methanol, decolorized with activated charcoal, and precipitated by addition of ether; yield 2.9 g (94 % based on Boc-Phe loaded resin) of *(3c)*. HPLC: content of *(3d)* <0.4 %.

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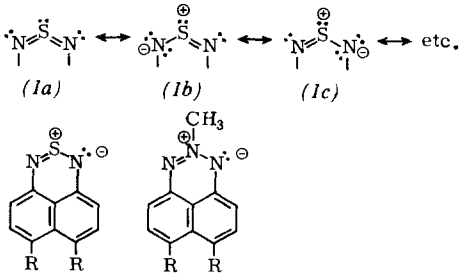
CAS Registry numbers:
(1a), 5609-55-2; *(1b)*, 66610-83-1; *(1c)*, 66653-18-7; *(1c)* HCl, 65864-23-5; *(1d)*, 66653-19-8; *(2)*, 530-62-1; *(3a)*, 66610-82-0; *(3b)*, 66610-81-9; *(3c)*, 66674-35-9; *(3d)*, 66610-80-8; *(4)*, 6160-65-2; *(5)*, 66653-20-1; *(6)*, 38678-68-1; *(7)*, 66610-79-5

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[3] a) *F. Wessely, K. Schlögl, G. Korger*, Monatsh. Chem. *83*, 1156 (1952); b) *R. Tomatis, S. Salvadori*, Farmaco, Ed. Sci. *32*, 592 (1977); c) *J. Pless*, J. Org. Chem. *39*, 2644 (1974); d) *F. Wessely, K. Schlögl, E. Wawersich*, Monatsh. Chem. *83*, 1439 (1952); e) *S. Goldschmidt, M. Wick*, Justus Liebigs Ann. Chem. *575*, 217 (1952).
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[5] Mass spectra: Dr. *H. J. Förster*, Ingelheim.
[6] Degradation: 3 N *p*-toluenesulfonic acid, 0.2% tryptamine, 110 °C, 20 h; cf. *T. Y. Liu, Y. H. Chang*, J. Biol. Chem. *246*, 2842 (1971).
[7] Degradation: 4.2 N NaOH, 3.3 % thiodiglycol, 110 °C, 72 h; cf. *T. E. Hugli, S. Moore*, J. Biol. Chem. *247*, 2828 (1972).

3d-Orbital Participation in Sulfur Diimides[**]

By *Richard Bartetzko* and *Rolf Gleiter*[*]

Whenever sulfur compounds exhibit unexpected physical or chemical properties, an expansion of the electron octet to a decet (participation of 3d orbitals in bonding) is invoked[1]. The relatively high stability of sulfur diimides *(1)* and their frequent occurrence as structural components of organic and inorganic compounds[2] have led to their formulation with tetravalent sulfur *(1a)*[3] although the ground state can just as well be described in terms of resonance between the charged forms *(1b)*↔*(1c)*.



(1a) *(1b)* *(1c)*

R

(2) H *(4)*
(3) CH_2– *(5)*

Comparison of electronic spectra in stretched films as well as photoelectron (PE) spectra of the naphtho[1,8-*cd*]thiadia-

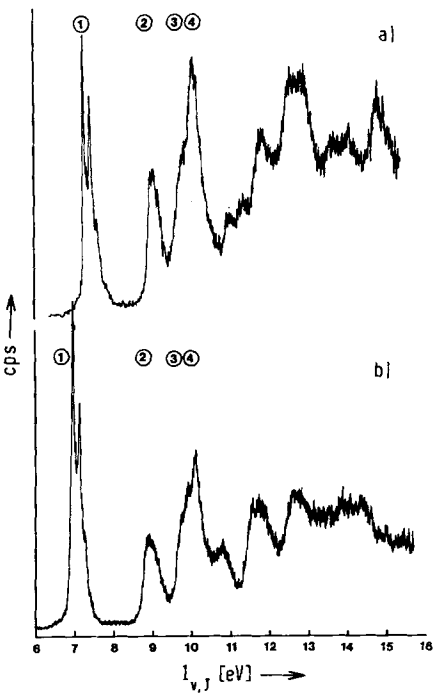


Fig. 1. PE spectra of (a) the thiadiazine *(2)* and (b) the triazine *(4)*. Band assignment was based on comparison with calculated (EH and MINDO/3 [6]) orbital energies; the $I_{v,j}$ values [eV] for *(2)* are ① 7.46, $a_2(\pi)$; ② 9.02, $b_2(n_-)$; ③ 9.90, $b_1(\pi)$; ④ 10.14, $a_1(n_+)$; and those for *(4)* are ① 6.79, a_2, $a_2(\pi)$; ② 8.65, $b_2(n_-)$; ③ 9.55, $b_1(\pi)$; ④ 9.82, $a_1(n_+)$ [7].

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[**] Electronic Structure of Sulfur Compounds, Part 29. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 28: *R. Gleiter, R. Bartetzko, G. Brähler, H. Bock*, J. Org. Chem., in press.

Table 1. Comparison of experimental absorption bands and calculated [8] electronic transitions of *(2)* to *(4)*.

Compound	Experiment				Calculation			
	Band	$\tilde{\nu}$ [cm^{-1}]	logε	Polarization	$\tilde{\nu}$ [cm^{-1}]	f	Polarization	Configuration
(2)	A	15550	2.74	—	13680	0.07	⊥	$\pi_1^*\leftarrow\pi_1$ (92%)
	B	28985	3.93	—	28736	0.18	⊥	$\pi_3^*\leftarrow\pi_1$ (76%)
	C	30300	3.92	—	30395	0.01	∥	$\pi_2^*\leftarrow\pi_1$ (92%)
	D	39210	4.07	—	40161	0.78	∥	$\pi_4^*\leftarrow\pi_1$ (81%)
	E	42735	4.73	—	44843	1.26	⊥	$\pi_2^*\leftarrow\pi_2$ (63%)
(3)	A	14705	2.62	—	11962	0.07	⊥	$\pi_1^*\leftarrow\pi_1$ (94%)
	B	24700	1.90	∥	25063	0.26	∥	$\pi_2^*\leftarrow\pi_1$ (79%)
	C	27930	3.96	⊥	27322	0.17	⊥	$\pi_3^*\leftarrow\pi_1$ (77%)
	D	30770	3.92	∥	30303	0.03	∥	$\pi_1^*\leftarrow\pi_3$ (92%)
	E	38460	4.22	∥	35510	1.27	∥	$\pi_2^*\leftarrow\pi_1$ (75%)
	F	42735	4.71	⊥	36765	0.11	⊥	$\pi_1^*\leftarrow\pi_4$ (82%)
(4)	A	16474	2.98	—	12469	0.07	⊥	$\pi_1^*\leftarrow\pi_1$ (92%)
	B	25974	3.37	∥	28011	0.12	∥	$\pi_2^*\leftarrow\pi_1$ (64%)
	C	28170	4.18	⊥	28818	0.16	⊥	$\pi_3^*\leftarrow\pi_1$ (75%)
	D	33330	2.76	∥	37313	0.83	∥	$\pi_1^*\leftarrow\pi_4$ (69%)
	E	43480	4.61	⊥	44843	1.25	⊥	$\pi_2^*\leftarrow\pi_2$ (64%)
(5)	A	16890	2.70	—	18827	0.07	⊥	$\pi_1^*\leftarrow\pi_1$ (94%)
	B	26000	—	∥	25268	0.27	∥	$\pi_2^*\leftarrow\pi_1$ (79%)
	C	26455	4.00	⊥	27714	0.17	⊥	$\pi_3^*\leftarrow\pi_1$ (77%)
	D	31150	3.76	∥	32940	1.67	∥	$\pi_1^*\leftarrow\pi_2$ (72%)
	E	41840	4.58	⊥	45118	1.12	⊥	$\pi_2^*\leftarrow\pi_3$ (60%)

zines *(2)* and *(3)*[4] as model substances for *(1)* with the corresponding spectra of the 2-methylnaphtho[1,8-*de*]triazines *(4)* and *(5)*[5], which cannot be formulated analogously to *(1a)*, shows the spectra to be almost superimposable (cf. Fig. 1 and Table 1).

The spectra were interpreted assuming (i) that the bands of the electronic spectra can be described as $\pi^*\leftarrow\pi$ transitions[8] and (ii) the validity of Koopmans' theorem ($-\varepsilon_j = I_{v,j}$). Within this framework, comparison of experimental data with calculated values (energy, intensity, direction of polarization; ionization potential and intensity) showed that the observed similarity between the spectra of *(2)*, *(3)* and those of *(4)*, *(5)* is due to analogous valence electron structures. Hence we conclude that valence structures with tetravalent sulfur can be neglected for *(1)*. In molecular orbital terms, this means that 3d orbitals are of no importance in the description of *(1)*, whether in the ground state or in excited states.

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CAS Registry numbers:
(2), 2609-05-4; *(3)*, 66515-30-8; *(4)*, 40237-01-2; *(5)*, 66515-36-4

[1] *H. Kwart, K. King:* d-Orbitals in the Chemistry of Silicon, Phosphorus and Sulfur. Springer-Verlag, Berlin 1977; references cited therein.

[2] *K. T. Potts* in *A. Weissberger, E. C. Taylor:* Special Topics in Heterocyclic Chemistry. Wiley, New York 1977; *C. R. Ramsden*, Tetrahedron *33*, 3203 (1977); *H. W. Roesky*, Z. Naturforsch. *B31*, 680 (1976); *E. M. Holt, S. L. Holt, K. J. Watson*, J. Chem. Soc. Dalton Trans. *1977*, 514; references cited therein.

[3] *J. Kroner, W. Strack, F. Holsboer, W. Kosbahn*, Z. Naturforsch. *B28*, 188 (1973); references cited therein.

[4] *H. Behringer, K. Leiritz*, Chem. Ber. *98*, 3196 (1965); *H. Beecken, ibid. 100*, 2164 (1967).

[5] *M. J. Perkins*, J. Chem. Soc. *1964*, 3005; *P. Tavs, H. Sieper, H. Beecken*, Justus Liebigs Ann. Chem. *704*, 150 (1967).

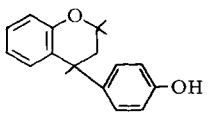
[6] EH: *R. Hoffmann*, J. Chem. Phys. *39*, 1397 (1963); *R. Hoffmann, W. N. Lipscomb, ibid. 36*, 2179 (1962); *37*, 2872 (1962); MINDO/3: *R. Bingham, M. J. S. Dewar, D. H. Lo*, J. Am. Chem. Soc. *97*, 1285 (1975).

[7] Another possible assignment of the bands ① to ④ in the PE spectra of *(2)* and *(3)* is $a_2(\pi)$, $b_1(\pi)$, $b_2(n_-)$, and $a_1(n_+)$. However, our arguments would be unaffected by this orbital sequence.

[8] The PPP-CI model was used with parameters taken from the literature for calculation of the electronic spectra; cf. *J. Fabian, A. Mehlhorn, R. Zahradník*, Theor. Chim. Acta *12*, 247 (1968); *J. Fabian*, Z. Chem. *9*, 99 (1969).

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

Crystalline clathrates in which the guest molecule is contained as within a cage are surveyed by *D. D. MacNicol, J. J. McKendrick*, and *D. R. Wilson*. The article is concerned mainly with cages made of the chroman *(1)* and related compounds. The cages made of molecules *(1)* are held together by hydrogen bonds between the OH groups; six O atoms form the roof and six the floor of the cage. Two small guest molecules

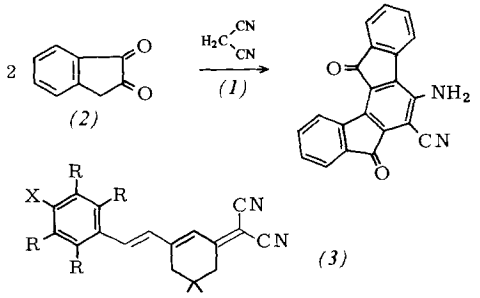


(1)

or one large one can be included in each of these cavities. Among other applications, *(1)* has been used as a matrix for studies on radicals generated *in situ*. Clathrates composed of *(1)* and SF_6 have been proposed for the storage and controlled liberation of this gas. [Clathrates and Molecular Inclusion Phenomena. Chem. Soc. Rev. 7, 65—87 (1978); 153 references]

[Rd 20 IE]

New applications of malononitrile *(1)* in organic chemistry are considered in a survey by *A. J. Fatiadi*. Two examples may be cited: (i) the coupling of 1,2-indandione *(2)* with



(2) *(3)*

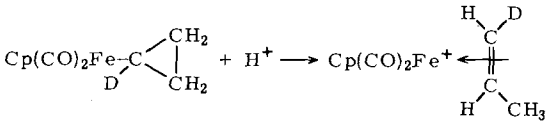
(1) in dimethylformamide and the synthesis of solvatochromic dyes *(3)* from substituted aromatic aldehydes, isophorone, and *(1)* (in DMF/piperidine/glacial acetic acid) by Knoevenagel condensation. [New Applications of Malononitrile in Organic Chemistry (in two parts). Synthesis *1978*, 165—204, 241—282; total of 589 references]

[Rd 17 IE]

Reactions between electrophiles and σ-bonded organotransition metal complexes are considered by *M. D. Johnson*. Three principal reaction types can be distinguished: 1) Reactions involving replacement of the metal by attack at the α-C atom, *e.g.*

$$ArCH_2Co(CN)_5^{3-} + NO^+ \xrightarrow{H_2O} Co(CN)_5^{2-} + ArCH_2NO \longrightarrow ArCH{=}NOH$$

2) Reactions with considerable modification of the C—M bond, *e.g.*



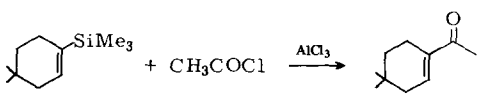
and 3) reactions with only slight modification at the C—M bond, *e.g.*

$$(4\text{-}H^+py)CH_2M + H_2O \rightleftharpoons pyCH_2M + H_3O^+$$

[Reactions of Electrophiles with σ-Bonded Organotransition Metal Complexes. Acc. Chem. Res. *11*, 57—65 (1978); 92 references]

[Rd 13 IE]

The role of silicon in organic chemistry is examined by *E. W. Colvin*. Substitution with silicon-containing groups provides a means of activating substrates or reagents, controlling their reaction course, or protecting the substrate from unde-



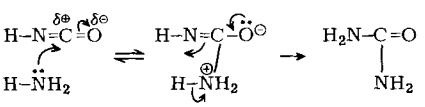
(1) *(2)*

sired reactions. An example is provided by the synthesis of the α,β-unsaturated ketone *(2)* from the vinylsilane *(1)* and acetyl chloride. [Silicon in Organic Synthesis. Chem. Soc. Rev. 7, 15—64 (1978); 250 references]

[Rd 19 IE]

The transformation of ammonium cyanate into urea—discovered 150 years ago by *Wöhler*—is known to all chemists on account of its historical importance. Less well known, according to *J. Shorter*, is the fact that the question of its mechanism has still not been settled although discussions began 80 years ago. Any decision between the ionic (a) and

$$NH_4^{\oplus} + CNO^{\ominus} \rightleftharpoons CO(NH_2)_2 \qquad (a)$$



(b)

the molecular mechanism (b) appears impossible on the basis of conventional kinetic methods. [The Conversion of Ammonium Cyanate into Urea—A Saga in Reaction Mechanisms. Chem. Soc. Rev. 7, 1—14 (1978); 69 references]

[Rd 18 IE]

Pericyclic Reactions. Vol. I. By *A. P. Marchand* and *R. E. Lehr*. Academic Press, Inc., New York—London 1977. 1st Edit., xi, 286 pp., bound $ 28.00.

Twelve years after appearance of *Woodward* and *Hoffmann*'s equally fundamental and stimulating work, *Marchand* and *Lehr* present the first volume of "Pericyclic Reactions". Selected aspects of this type of reaction are set out and looked at critically in four chapters.

The first chapter, "Operational Criteria for Evaluation of Concertedness in Potential Pericyclic Reactions", written by *Lehr* and *Marchand*, is concerned with the experimental criteria that can lead to a statement whether or not a reaction course is concerted. As examples, kinetic and thermodynamic results, investigations of isotope effects, and labeling experiments illustrate the textual content.

The second Chapter, "The Möbius-Hückel Treatment of Organic Systems and Reactions and MO Following as a Technique in Organic Chemistry", written by *H. E. Zimmerman*, is fully in line with the intention laid down in the first sentence of the article: "The present chapter presents the author's approach to dealing with orbital-control of organic reactions". Correspondingly, for instance, *Fukui*'s name is not mentioned in the references. If this article is designed to give an insight into the theoretical background to pericyclic reactions, we cannot deny that this brilliantly written chapter has a certain onesidedness. It may be added that the Möbius-Hückel procedure is also known as the Evans-Dewar procedure.

W. M. Jones and *U. H. Brinker* contributed the third Chapter, "Some Pericyclic Reactions of Carbenes". The accent is placed on addition to multiple bonds, insertion into C—H bonds, and 1,2-rearrangement of carbenes, in which besides experiments the qualitative and quantitative theoretical approaches to these reactions are discussed. Rearrangement of vinylcarbenes to cyclopropenes is reviewed for the first time. Special weight is also laid on sections about carbene-carbene rearrangements and on ring-opening of cyclopropylidenes to allenes.

"Pericyclic Reactions of Carbanions" is the title of the fourth Chapter, by *S. W. Staley*. In this review of a topical and rapidly developing field are included the rotation barriers of unsaturated "carbanions" as well as the typical pericyclic reactions; this feature is especially welcome, since stereochemical investigations in these species depend far more than *e.g.* investigations in olefins on comparatively low rotation barriers. One can be excited to learn how investigations of the ion-pair character and of reversible electron-transfer processes will widen our knowledge of this field.

All in all, this is a volume of reviews of important areas for those familiar with the field. It also provides any interested chemist with an expert introduction.

Gernot Boche [NB 418 IE]

Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel (Chemistry of Pesticides and Plant-Protection Agents). Edited by *R. Wegler*. Vol. 5. Herbicides. Technical editors: *R. Wegler* and *L. Eue*. Springer-Verlag, Berlin—Heidelberg—New York 1977. xxi, 752 pp., 6 figs., bound, DM 198.—.

In the Foreword the editor bases his purpose on the need to use chemicals for plant protection; the efforts to produce vegetable foods as cheaply as possible and in good quality have led to a remarkable expansion of the spectrum of active agents, a feature applying particularly to fungicides. Among the herbicides there have been no essentially new discoveries of active substances to report recently, and yet the number of preparations on the market has greatly increased. In countries engaged intensively in agriculture, herbicides now account for more than half of all plant-treatment agents by amount and by value.

The usual division into inorganic and organic herbicides is retained in the present book. There are short introductory chapters on the mode of action and application as well as on tests, and a list of the various names used for weedkillers in the literature, particularly in patents. Inorganic compounds are mainly suitable for total weed destruction, and are still widely used despite the fact that their importance has been diminishing for several years. The authors have therefore confined their treatment to a few pages. Much space is given, on the other hand, to a description of organic herbicides. They are classified according to active components, a typical formula being provided for the various active compounds. In each case there follows a collection of the more recent literature and valid patents. A review of the supplementary patents published in 1969 to 1976 is given in a separate Appendix of over 300 pages. In the authors' view a comprehensive knowledge of the patent situation constitutes the basis for decisions about new developments and investment in plant. In view of the large number of herbicidal compounds described, the concluding subject and compound index is a valuable addition to the book.

Unlike earlier volumes in this series, the herbicide volume is produced photomechanically, which means that the reproduction of the formulas has suffered somewhat. However, the editor sees a special advantage in the possibility of continuing supplements, and in view of the continuing development of the herbicide sector this must be accepted, though with reservations. The book fulfils its purpose of providing detailed information for specialists in the chemical industry and for phytopathologists.

Dieter Knösel [NB 409 IE]

The Chemical Physics of Surfaces. By *S. R. Morrison*. Plenum Press, New York—London 1977. xvii, 415 pp., numerous figs. and tables, bound, $ 47.40.

An ever-increasing interest in the physics and chemistry of solid surfaces is currently fostered by the recent investigations of the use of semiconductors for the conversion of sunlight into electrical or chemical energy. Corrosion, catalysis, and electrophotography are other examples in which electron transfer at solid surfaces plays a part.

The author has been at pains—and with success—to bring the physicist's predominantly energetic mode of consideration (band model and surface states) into harmony with the chemist's mainly atomistic picture (surface groups, active centers). At last, someone has pointed out that there is a difference between redox processes and Lewis acid-base reactions. Of course, Lewis base centers may occasionally donate single electrons. The first chapter reads like a good textbook and provides the chemist with an excellent introduction. With didactic skill of high order the principles are first described and discussed qualitatively, then treated formally and quantitatively. In the energy level diagrams the coordinates are clearly marked, which is a pleasant change. The text could, however, have been supported by more illustrations. The real structure of crystal surfaces is treated too briefly. The exposition of the experimental methods is comparatively short, and owing to the rapid development of this field it is not completely up

to date. Above all, a more detailed description of how to determine band edge energies and flat band potentials would have been welcome.

In line with the author's interests, the description of individual systems is dominated by semiconductors and ionic crystals, while metals are treated rather summarily. This part of the book contains a compressed review of recent literature; the last chapter, on heterogeneous catalysis, can naturally provide only a limited selection. The sections on solid/solution interfaces and on photoeffects on semiconductor surfaces are highly informative. The rich bibliography goes up to the end of 1975.

The book will undoubtedly prove extremely useful to the chemist who wants to work his way into problems of solid surfaces; his own background will enable him to go beyond the summary and the simplified descriptions in the field of chemistry. Pure physicists will find the book harder to digest.

Hanns-Peter Boehm [NB 410 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Organometallic Reactions and Syntheses, Vol. 6. Edited by *E. I. Becker* and *M. Tsutsui*. Plenum Press, New York 1977. xi, 314 pp., bound $ 47.40.—ISBN 0-306-39906-7

Inorganic Reaction Mechanisms, Vol. 5. Senior Reporter: *A. McAuley*. The Chemical Society, London 1977. xviii, 454 pp., bound £ 29.00.—ISBN 0-85186-295-0.—A volume in the series "Specialist Periodical Reports"

Phase Equilibria and Fluid Properties in the Chemical Industry. Estimation and Correlation. ACS Symposium Series 60. By *T. S. Storvick* and *S. I. Sandler*. American Chemical Society, Washington 1977. xiii, 537 pp., bound $ 32.00.—ISBN 0-8412-0393-8

Optoacoustic Spectroscopy and Detection. Edited by *Yoh-Han Pao*. Academic Press, New York 1977. xi, 244 pp., bound $ 19.00.—ISBN 0-12-544150-9

Methods in Immunology. A Laboratory Text for Instruction and Research. By *J. S. Garvey, N. E. Cremer*, and *D. H. Sussdorf*. W. A. Benjamin, Reading 1977. 3rd revised and enlarged edition. xxiii, 545 pp., bound $ 27.50.—ISBN 0-8053-3125

Advances in Carbohydrate Chemistry and Biochemistry, Vol. 34. Edited by *R. S. Tipson* and *D. Horton*. Academic Press, New York 1977. x, 439 pp., bound $ 42.50.—ISBN 0-12-007234-3

IUPAC: Chemistry of Natural Products—10 (Dunedin, 1976). Edited by *A. D. Campbell*. Pergamon Press, Oxford 1978. pp. 1241–1436, bound DM 105.—.—ISBN 0-08-021198-4

IUPAC: Physical Organic Chemistry—3 (Montpellier, 1976). Edited by *A. Fruchier*. Pergamon Press, Oxford 1977. pp. 963–1067, bound $ 17.00.—ISBN 0-08-021197-6

Gmelin Handbuch der Anorganischen Chemie, Springer-Verlag, Berlin 1978. 8th Edit.

Hauptwerk, System-Nr. 14: Carbon. Part D: The Compounds. Instalment 6: Carbon-Sulfur Compounds (continued). Carbon-Selenium and Carbon-Tellurium Compounds. xxxii, 264 pp., bound DM 641.—.—ISBN 3-540-93356-5

Ergänzungswerk, Band 47: Organobismuth Compounds. xviii, 173 pp., bound DM 432.—.—ISBN 3-540-93349-2

Ergänzungswerk, Band 50: Organoiron Compounds. Part A: Ferrocene 3. x, 180 pp., bound DM 441.—.—ISBN 3-540-93354-9

Hauptwerk, System-Nr. 46: Tin. Part C: The Compounds. Instalment 6: Complex Compounds of Tin (contd.). Molecular Formalae and Alphabetical Index for Part C 5 and 6. xx, 236 pp., bound DM 521.—.—ISBN 3-540-93357-3

Gmelin Handbuch der Anorganischen Chemie, Springer-Verlag, Berlin 1977. 8th Edit.

Ergänzungswerk, Band 48: Boron Compounds. Part 16: Boron-Oxygen Compounds 2. xviii, 221 pp., bound DM 571.—.—ISBN 3-540-93353-0

Hauptwerk, System-Nr. 11: Tellurium. Part B: The Compounds. Instal. 2: Compounds with Fluorine and Chlorine. xviii, 152 pp., bound DM 373.—.—ISBN 3-540-93352-2

Ergänzungswerk, Band 49: Organoiron Compounds. Part A: Ferrocene 2. Instal. 2: Mononuclear Monosubstituted Ferrocene Derivatives with O-Containing Substituents, Part 1: Alcohols, Phenols, Carboxylic Acid Esters of the fc-AOOC-R Type, Ethers, Aldehydes, and Ketones of the fc-CO-R Type. xii, 303 pp., bound DM 687.—.—ISBN 3-540-93350-6

Hauptwerk, System-Nr. 47: Lead. Part A: History. Occurrence. Instal. 2b: Magmatic Cycle. xvi, 276 pp., bound DM 681.—.—ISBN 3-540-93024-8

Hauptwerk, System-Nr. 51: Protactinium. Suppl. Vol. 2: Metal. Alloys. Compounds. Chemistry in Solution. xxii, 337 pp., bound DM 731.—.—ISBN 3-540-93355-7

Hauptwerk, System-Nr. 53: Molybdenum. Suppl. Vol. Part A 1: Metal, Technology. xiv, 207 pp., bound DM 503.—.—ISBN 3-540-93348-4

Index: Formula Index, Vol. 7: C_{24}–Ca. xv, 293 pp., bound DM 672.—.—ISBN 3-540-93351-4

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Reflections on an Anniversary of Chemical Synthesis

By Gerhard Quinkert[*]

Dedicated to Sir Derek Barton on the occasion of his sixtieth birthday

The significance of chemistry as a science and as a branch of industry, as well as its role in the evolution of scientific thought during the past 150 years, are thoughts which come to mind while contemplating the development of organic synthesis.

1978 is an anniversary of chemical synthesis.

- 150 years ago *Wöhler* reported "Über künstliche Bildung des Harnstoffs" from ammonium cyanate[1];
- 100 years ago *Baeyer* delivered his famous speech "Über die chemische Synthese"[2];
- 50 years ago *Diels* and *Alder* added the cycloaddition bearing their names[3] to the existing armamentarium of synthetic methods.

Retracing the pathway leading from the events indicated up to the present day reveals the way in which chemical synthesis has evolved. In his searching study on "La logique du vivant"[4] *François Jacob* has taken note of the role organic chemistry played in the first part of the 19th century. The task of this discipline was to analyze. This branch of science had to identify the substances of life and to unravel their "metamorphosis" in the organs and organisms. Synthetic contributions were not expected. Only living organisms were thought to be able to build up the chemical materials of life, by means of some vital force.

It is nowadays common knowledge that

- there is no biological basis for a special position of organic chemistry,
- there is no purely chemical way of deciding whether a compound has been synthesized in a cell or in a chemist's laboratory.

It is *Wöhler*'s conversion of ammonium cyanate into urea which caused such a change of mind. This event of the year 1828 determined the date of birth of organic chemistry as a science[5] and is even recognized as a turning point in the history of human knowledge[2].

> Konnte man den Harnstoff künstlich darstellen, so gab es keine Schranke mehr zwischen organischer und unorganischer Welt und mit frohem Erstaunen sah man der experimentellen Forschung die Möglichkeit eröffnet, die zahllosen Stoffe des Pflanzen- und Tierreichs künstlich darzustellen, vielleicht sogar – wenn auch nur in später Zukunft – das große Rätsel zu lösen, welches wir Leben nennen[2]

Such a hope does not seem presumptuous. Meanwhile *Khorana* by synthesizing well defined nucleic acids contributed to the decipherment of the genetic code[6]. Shortly afterwards he succeeded in the chemical synthesis of a gene[7]. To raise the question about the chances of synthesizing a living cell is no longer a prerogative of science fiction literature. In a state of the art account of the life sciences it was stated:

> Those who are hopeful about synthesizing a cell in the foreseeable future have every reason to retain their optimism[8].

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Wöhler's artificial formation of urea released chemical synthesis from its dogmatic fetters. The resulting consequences for thought and action are emphasized up to our days. It is thus all the more surprising that popular accounts of the historic event are often marred by a lack of attention to chemical detail[9-11].

During the "Gründerjahre", a short period of history immediately following the Franco-German War, there was literally a fortune to be made from chemical synthesis. Ample funds for investment, an optimistic faith in progress, and universities which had for some time been devoted to research and cultivated a tradition of excellence were all to be found within the boundaries of Germany[12-14]. The world-wide political activities of various neighboring states and their "industrial revolutions" had passed this country by. When industrialization at last began to gather momentum, chemistry proved to be one of the main driving forces. The principal reason for this turn of events was the existence of a viable research establishment which rose to the task of synthesizing valuable substances from inexpensive raw materials. Once *Liebig* had introduced the chemical laboratory into German universities, it was these institutions which fostered technological development. They provided adequate numbers of well trained chemists who mastered the handiwork of research. Notable university scholars consolidated and extended the foundations of chemistry, yet never losing sight of the economic significance of synthetic chemistry which provided additional incentive for their investigations. Pure research in German universities has always provided fertile ground for applied research and technological development[15]. It is therefore hardly surprising that *A. von Baeyer* received the Nobel prize in 1905 "for his services in the advancement of organic chemistry and the chemical industry"[16]. The same expression was to be used once again five years later when the Nobel prize was awarded to *O. Wallach*[16].

The official citation on the award of the Nobel prize to *R. B. Woodward* in 1965, *i.e.* "for his outstanding achievements in the art of organic synthesis"[17], enjoys the same pointedness as those just mentioned. *Woodward*'s syntheses of natural products belong to the great cultural contributions of our age, and provide a measure of the potential of organic chemistry. A branch of science which can accomplish the synthesis of chemical compounds possessing extremely complex structures is clearly in a healthy state:

> The synthesis of substances occurring in Nature, perhaps in greater measure than activities in any other area of organic chemistry, provides a measure of the condition and powers of the science. For synthetic objectives are seldom if ever taken by chance, nor will the most painstaking, or inspired, purely observational activities suffice. Synthesis must always be carried out by plan, and the synthetic frontier can be defined only in terms of the degree to which realistic planning is possible, utilizing all of the intellectual and physical tools available[18].

If proof were ever needed of the fruitful interplay that can take place between theoretical chemistry and practical chemical synthesis[19], it would be forthcoming from the publication of the now famous Woodward-Hoffmann rules[20] in the same year as *Woodward* received the highest scientific honor for his synthetic work. The synthesis of natural products now plays a leading role in the development of structural organic chemistry and the study of organic reactions[21,22]. The full implications of this are apparent from the two syntheses of vitamin B_{12} due to *Woodward* and *Eschenmoser*[23-25] and to *Eschenmoser*[26,27]: the synthetic target is particularly complex in its constitution and stereostructure. Its vitamin function lent it additional attraction. Since the structure had been determined by X-ray diffraction, its synthesis had to be planned from the very outset as an expedition through chemical *terra incognita*. The gigantic task was solved in a new spirit. The synthesis of natural products had meanwhile been relieved of the burden of structural confirmation, and nothing stood in the way of designing a synthetic strategy such that it could accommodate hitherto unknown but desired reactions in the course of its execution:

> The execution of such a synthesis is not simply an experimental verification of a plan conceived in detail in advance. Rather, in its most important phases it is an inquiry, guided by a synthetic strategy, into the reactivity of structural types with respect to their potential as intermediates in a synthetic reaction sequence. What the synthetic target provides is stimulation and direction. Challenged by the necessity of moving toward a given structure, the synthesis often leads to problems that are complementary to those chosen in open-ended preparative research on reactivity[22].

As the significance of chemical synthesis has grown, so too has the need to make known the problems of planning and executing syntheses and to concentrate more on teaching approaches to their solution. The time is ripe for such a shift in emphasis. There has been a recent boom in the literature devoted to the compilation[28,29], classification, and comparison[30-36] of synthetic methods for complex chemical compounds. Books are also being published which concentrate on the strategy and tactics of synthesis[37-40]. Much of the initiative in the systematic development of a synthetic methodology has been provided by *Corey*:

> A sufficiently great number and variety of syntheses have now been completed to encourage attempts at setting down in a generalized form the process by which a synthetic chemist devises an original but valid synthetic route to a complicated structure. Such an effort surely is more than an intriguing theoretical exercise: it is a prerequisite to a deeper comprehension of Synthesis and the methodologies which are fundamental

to it, and it is likely to be a keystone in the rational development of Synthesis to still higher forms. For example, any technique for the automatic generation of synthetic schemes by a computer will require a complete and detailed definition of the elements of Synthesis and their mutual interaction, in a most general sense[41].

Discussions about computer planning of syntheses are very evident in the literature[42–51] and in practice[52–54]. Opinion is divided, but most chemists would agree that

even if the effort to devise an effective problem-solving computer program were to fail utterly, a deeper comprehension of the strategies, principles, and elements of chemical synthesis would be gained, the classification and organisation of basic chemical data according to the requirements of synthesis would be advanced, and new and more powerful methods of teaching chemical synthesis and solving synthetic problems would result[43].

Although many reactions are known for the construction of carbon atom skeletons and/or introduction of functional groups, the search for new synthetic methods continues—with considerable success. The systematic study of a given class of compounds or a selected kind of reaction still plays a major role. A prototype of such a study is the 50-year old Diels-Alder reaction[55]. Wherever a six-membered ring occurs as a partial structure, whether in the target compound itself or in a projected precursor, the Diels-Alder reaction springs to mind. Time and again this cycloaddition has been utilized in the synthesis of natural products, with overwhelming success especially in cases where its regio- and particularly its stereoselectivity could be exploited.

The successful synthesis of a gene or of vitamin B_{12} could create the false impression that there is no longer any need for further methods of specific structural modification. Compared with the synthetic capabilities of Nature, most of our laboratory procedures leave much to be desired, particularly on account of the extreme conditions often required and their frequently inadequate regio-, stereo-, and enantio-selectivities[56–58].

From Molecular Biology we know that Nature is capable of carrying out Syntheses which are thousands of steps in length with a yield and an optical specificity of 100% in each step. We are very far from any such feat. The best industrial syntheses may attain average yields of over 90% for a 30–40 step synthesis. It is clear, therefore, that the synthesis of natural products remains an objective of great scientific value and of great social and economic significance[59].

In this anniversary year, there is every reason to intensify our efforts in the field of organic synthesis: The directed synthesis of improved products having desired properties continues to have a powerful economic incentive. The discovery of new synthetic reagents and the development of new preparative methods are still urgent problems of pure chemical research. Last but not least, the character-forming influence that active participation in a synthetic project aimed at a complex target structure may have on young scientists should not be underestimated.

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Intramolecular Ene Reactions in Organic Synthesis

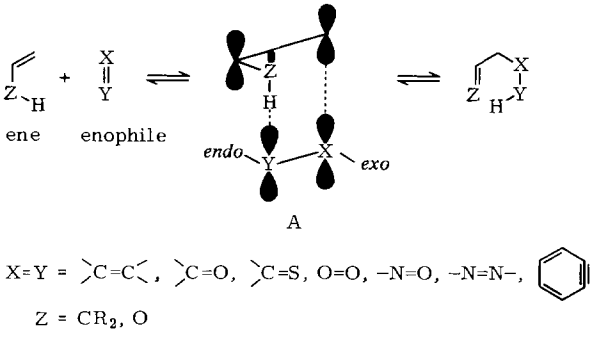
New synthetic methods (22)

By Wolfgang Oppolzer and Victor Snieckus[*]

Thermal cyclizations of appropriate dienes, enynes, enones and related unsaturated systems, some of them carried out on an industrial scale, demonstrate increasingly the preparative power of the intramolecular ene reaction. A variety of substituted, fused and bridged ring systems, including natural products, are thus easily accessible in a regio- and stereo-selective manner. Numerous examples are discussed systematically illustrating the possibilities, limitations, and common features of this cyclization reaction and its reverse ring-opening process.

1. Introduction

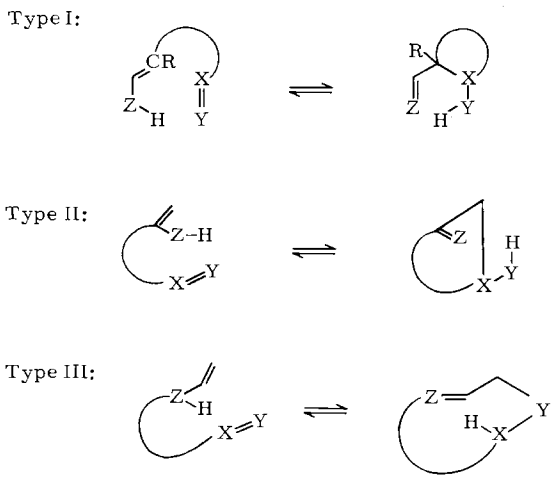
The ene reaction, first recognized and systematically investigated nearly 35 years ago by Alder[1], usually involves the thermal reaction of an olefin containing an allylic hydrogen (ene) with an electron-deficient multiple bond (enophile) to form a 1:1 adduct as illustrated in Scheme 1. Experimental evidence[2] and orbital symmetry considerations[3] are consistent with a concerted pathway involving a *supra-supra*facial *endo*- or *exo*-oriented interaction (see A). It thus resembles the Diels-Alder reaction[4] and [1,5] sigmatropic shifts[4,5], which are also considered to involve a cyclic 6e transition state. Recent calculations concerning the ene process[3] suggest that in the transition state A the C—X bond is more developed than the H—Y bond. (For related discussions regarding an unsymmetrical transition state in the Diels-Alder reaction see[6].) Mechanistic and preparative aspects of the ene reaction were comprehensively reviewed by *Hoffmann* in 1969[7] (see also[8]).



Scheme 1. The intermolecular ene reaction.

Early examples of the intramolecular ene reaction (Scheme 2) date back to the 1930's[9–11]; however, its synthetic utility has become recognized only recently parallel to the general interest in intramolecular [4+2][12–14] and [3+2][14,15] cycloadditions. Similar to the cycloadditions, the intramolecular ene process profits from entropic advantage and exhibits preparatively useful regio- and stereoselectivity. This applies to three different modes of thermally-induced cyclizations (and cycloreversions) (Scheme 2) in which the enophile is linked by an appropriate bridge, either to the olefinic terminal (Type I), the central atom (Type II), or the allylic terminal (Type III) of the ene unit.

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Scheme 2. Variants of the intramolecular ene reaction (Type I, Type II and Type III).

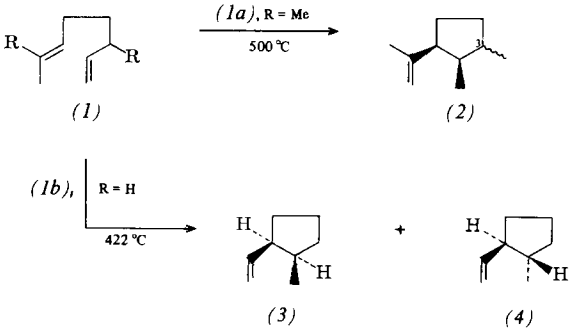
The aim of this review—in continuation of a review on intramolecular cycloadditions[14]—is to delineate the common characteristic features of the intramolecular ene reaction and to show, by selected examples, its scope, limitations, and utility in organic synthesis.

2. Type I Additions

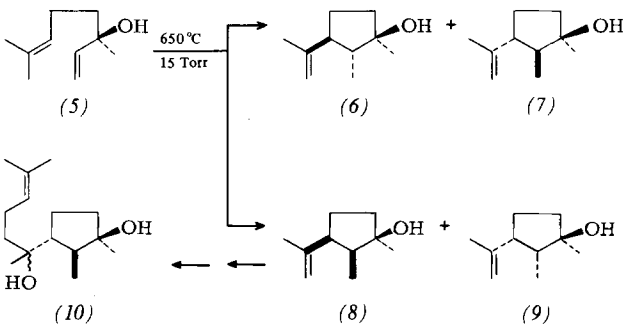
2.1. 1,6-Dienes

2.1.1. Acyclic 1,6-Dienes

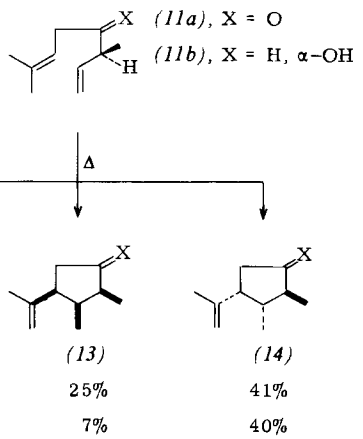
The majority of intramolecular ene reactions are concerned with the thermolysis of 1,6-dienes. In the first systematic study, *Huntsman* showed[16] that 1,6-dienes undergo cyclization to vinyl cyclopentanes, *e.g.* *(1a)*→*(2)*. This demonstrated the effective participation of nonactivated double bonds in the intramolecular ene process in contrast to the necessity for activated enophiles in the bimolecular counterpart. That this effect may be due to entropic factors is evident from the less negative entropy of activation ($\Delta S^{\neq} = -18$ cal K^{-1} mol^{-1}) for the reaction *(1a)*→*(2)* compared with that for intermolecular cases ($\Delta S^{\neq} = -30$ to -45 cal K^{-1} mol^{-1}[12b, 7]). Furthermore, this example illustrates the regioselectivity observed for numerous intramolecular ene reactions of 1,6-dienes in that predominant C—C bond formation occurs between the *closest* olefinic termini leading to five-membered rings. In addition, stereochemical selectivity was displayed in that cyclization of *(1a)* yielded a 4:1 mixture of the C(3)-epimers *(2)*[17] and also ring closure of *(1b)* gave *(3)* and *(4)* in the ratio 14:1[16].

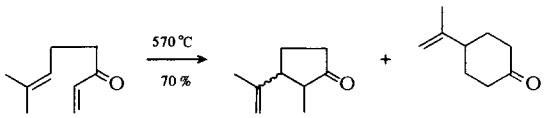


The analogous thermolysis of linalool *(5)* to give the plinols *(6)*—*(9)* was first carried out by *Ikeda* in 1936[11] and more carefully investigated by *Ohloff* 30 years later[18]. Flash pyrolysis of *(5)* at 650°C under reduced pressure gave a 9:15:50:26 mixture of all four possible diasteriomeric plinols *(6)* to *(9)* in high yield, again indicating high regioselectivity but considerable loss of stereochemical control. In fact, a recent careful study has shown[19] that thermolysis of *(5)* under kinetically controlled conditions at lower temperature affords almost exclusively *(8)* and *(9)*. Thus, vapor phase pyrolysis (240 to 290°C) of the silylether of *(5)* (so as to avoid the partial dehydration occurring with *(5)*) showed the kinetic parameters $\Delta S^{\neq} = -18.7$ to -19.4 cal K^{-1} mol^{-1}, $\Delta H^{\neq} = 31.2$ to 31.8 kcal mol^{-1} and $\Delta G^{\neq} = 32.3$ to 32.9 kcal mol^{-1} for the formation of *(8)* and *(9)* which is favored over the formation of *(6)* and *(7)* by a difference $\Delta\Delta G^{\neq} = 2.2$ to 3.1 kcal mol^{-1}. Therefore the earlier observed formation of the products *(6)* and *(7)* at 650°C[18] may be attributed to the reversibility of the reaction at the higher temperature. The synthetic utility of such cyclizations is demonstrated[20] by the conversion of the main product *(8)* into the fungal sesquiterpene cyclonerodiol *(10)*.



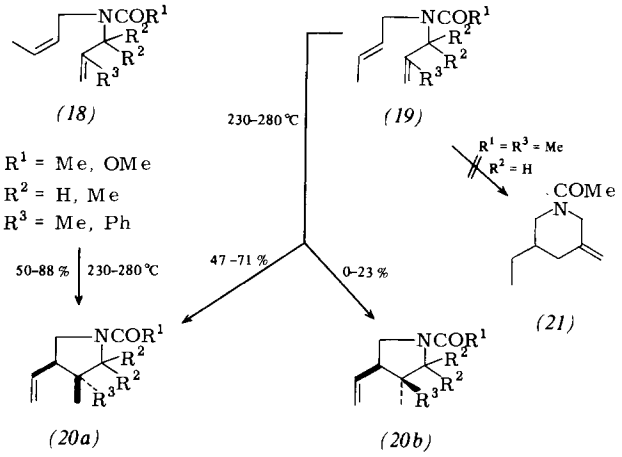
Thermolysis of the structurally similar dienes *(11a)* and *(11b)* likewise results in almost exclusive formation of cyclopentanes *(13)* and *(14)* with *cis* oriented adjacent isopropenyl and methyl groups at C-4 and C-3[21]. On the other hand, loss of regioselectivity was observed in the pyrolysis of the dienones *(15)*, leading to the cyclopentanones *(16a)* and *(16b)* together with the cyclohexanone *(17)* in the ratio 2:3:1[22]. At 570°C, partial interconversion of *(17)* and *(16)* was observed, again indicating the operation of a retro ene-process.



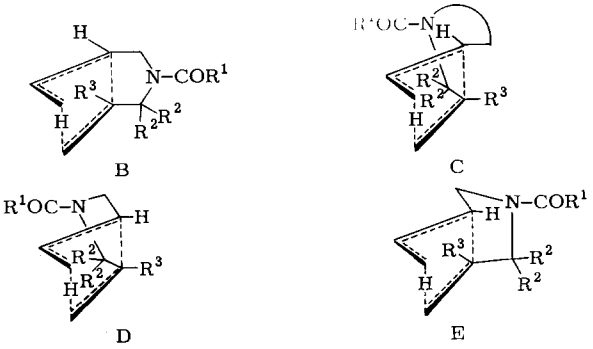


(15) (16a), cis (16b), trans (17)

The first systematic stereochemical investigation[23] of the intramolecular ene reaction dealt with the regioselective thermal cyclization of the *N*-allyl-*N*-(2-butenyl)amides *(18)* and *(19)* to afford the *cis*-substituted pyrrolidine derivatives *(20a)* in high yields. The *cis* dienes *(18)* reacted under kinetic control with 100% stereoselectivity whereas the *trans* dienes *(19)* furnished, in addition to *(20a)*, minor amounts of the *trans* isomers *(20b)*. Model considerations (Scheme 3) show that the observed stereochemical results are consistent with a *supra-supra*facial process. In the cyclization of the *cis* diene *(18)*, the *endo* transition state C appears to be highly strained thus favoring the exclusive formation of the *cis*-substituted pyrrolidine *(20a) via* the relatively unstrained *exo* transition state B.

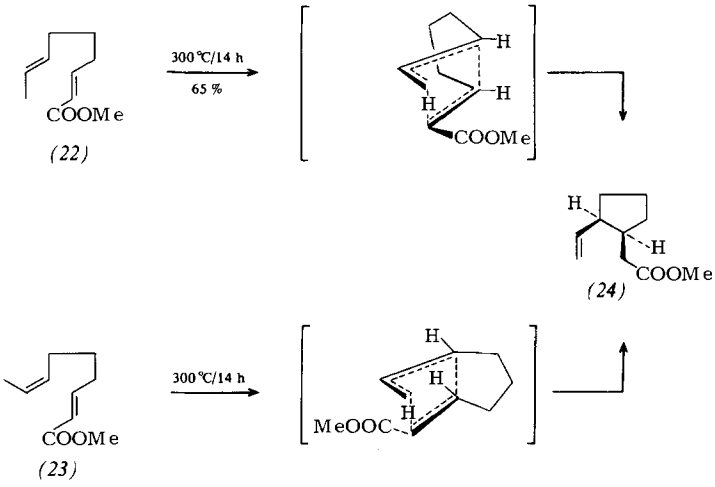


In the analogous cyclization of the *trans* diene *(19)*, preference of the *endo* transition state D over the *exo* transition state E is indicated. From these studies, it also appeared that not only the stereochemical outcome but also the rate of the intramolecular ene reaction of 1,6-dienes may be largely independent of the ene geometry.

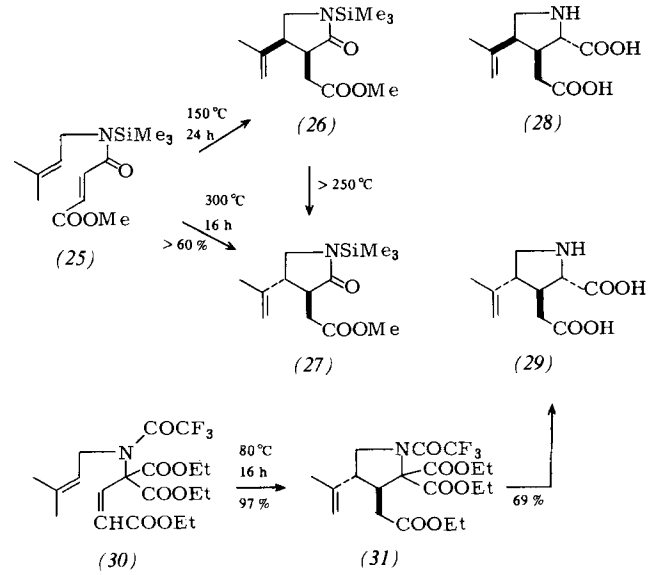


Scheme 3. Transition states for the thermal cyclizations of the dienes *(18)* and *(19)*.

Similarly, at 300 °C, both the terminally carbonyl-conjugated *trans,trans* diene *(22)* and its *cis,trans* isomer *(23)* provided the *cis*-substituted cyclopentane *(24)* at the same rate thus indicating no preference for an *endo*-oriented methoxycarbonyl group in the transition state[24].

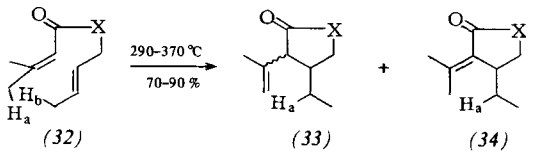


In an attempt to synthesize the natural anthelminthics, α-kainic acid *(28)* and α-allokainic acid *(29)*, cyclization of the readily available fumaric ester amide *(25)* was examined[25]. At 150 °C, the *cis*-pyrrolidone *(26)* was the exclusive product; on the other hand, thermolysis of the diene *(25)* or *(26)* at higher temperature furnished predominantly the thermodynamically more stable *trans* isomer *(27)*. This finding demonstrates the possibility of selectively synthesizing both *cis*- and *trans*-substituted five-membered rings under conditions of kinetic or thermodynamic control. The conversions *(26)* → *(28)* and *(27)* → *(29)* have not yet been realized; however, the natural amino acid *(29)* has been prepared in good yield from the simple precursor *(30)* in two synthetic operations[25]. The key step *(30)* → *(31)* proceeds in quantitative yield at surprisingly low temperatures (80 °C/16 h or 25 °C/3 months). Whether or not the exclusive formation of the *trans*-substituted pyrrolidine *(31)* is due to the reversibility of the reaction remains to be clarified.



The analogous cyclizations of the diene amides, esters, and ketones *(32)* with carbonyl-conjugated ene units provide stereo

and double bond isomers *(33)* and *(34)* in good yields and thus indicate preference for H_a over H_b hydrogen transfer[26]. (An alternative explanation for this preference involves hydrogen transfer *via* a dienol intermediate by a Type II ene reaction.)

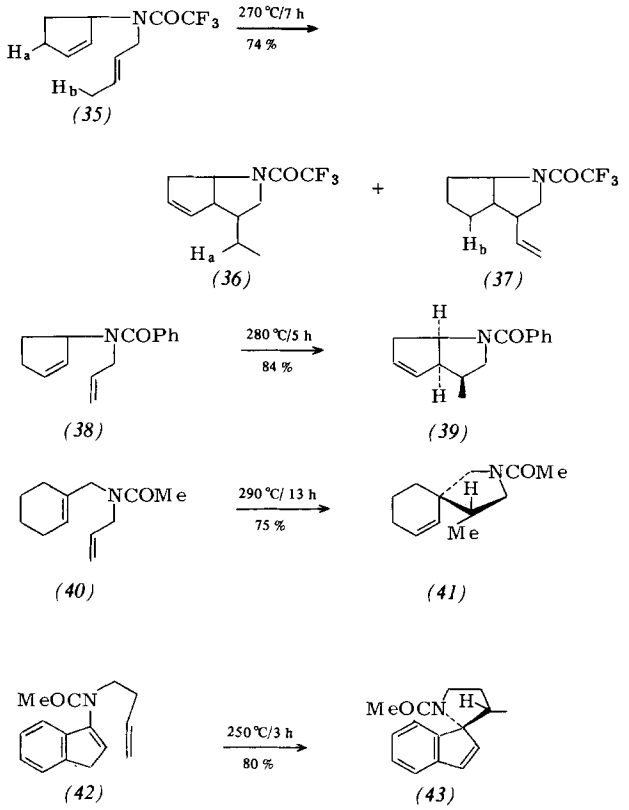


(32) *(33)* *(34)*

(a), X = NH, NR; *(b)*, X = O; *(c)*, X = CH_2

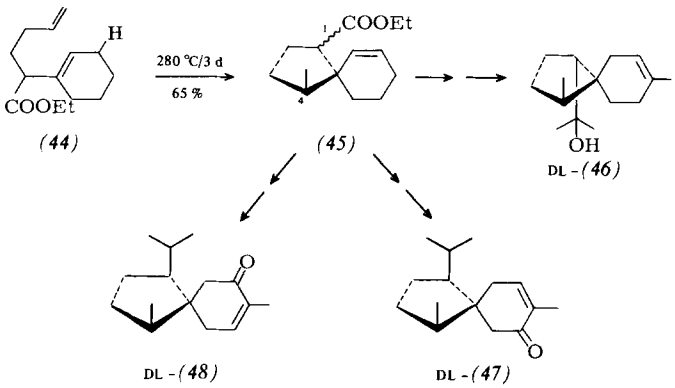
2.1.2. Cyclic 1,6-Dienes

Cyclic dienes in which one double bond is situated in the ring and the other in a side chain can likewise undergo intramolecular ene reactions. In contrast to the reaction *(32)* → *(33)* + *(34)* essentially no discrimination in the transfer of H_a and H_b was observed in the thermolysis of the cyclopentenylamide *(35)* to give the structural isomers *(36)* and *(37)*[23]. However, 1,6-dienes containing an endocyclic ene component and a terminal olefin as enophile unit, cyclize efficiently to single bicyclic products. Thus the highly stereoselective transformations *(38)* → *(39)*, *(40)* → *(41)*, and *(42)* → *(43)* illustrate nicely a simple route to fused or spiro bicyclic systems containing *cis*-related methyl- and vinyl substituents[23].

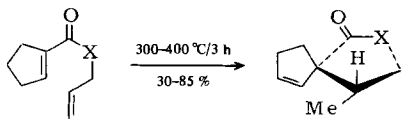


(35) *(36)* *(37)* *(38)* *(39)* *(40)* *(41)* *(42)* *(43)*

These stereochemical features, which are also observed in the thermal cyclization of open chain dienes (see Section 2.1.1), have been exploited in a flexible and stereoselective approach to spirosesquiterpenes[27]. Thus the readily available cyclohexenyl derivative *(44)* cyclizes at 280 to 290 °C exclusively to the C-1 epimeric *endo* products *(45)*. Their base-induced interconversion provides easy access to either 1,4-*trans* or 1,4-*cis*-substituted natural spiro[4,5]decanes[27d] such as β-acorenol *(46)*[27a], acorenone-B *(47)*[27b] and acorenone *(48)*[27c]. Similar stereoselective formation of spiro-lactams, -lactones, and -ketones *(50)* is observed on heating compounds *(49)* at high temperatures[26].



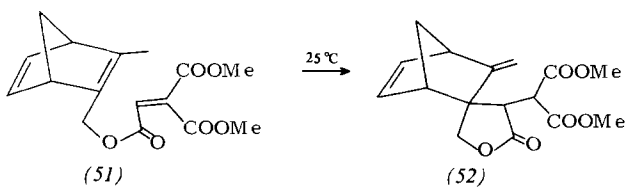
(44) *(45)* DL-*(46)* DL-*(48)* DL-*(47)*



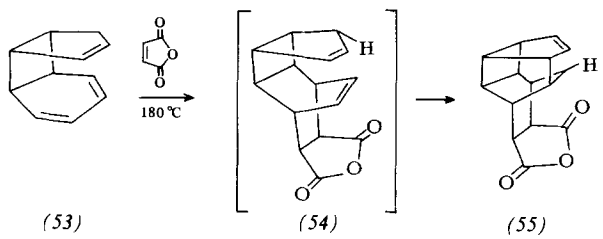
(49) *(50)*

(a), X = NR; *(b)*, X = O; *(c)*, X = CH_2

Activation of the enophile component by three carbonyl groups as in *(51)* promotes smooth cyclization even at room temperature to give a single spirolactone *(52)*, the stereochemistry of which has not yet been elucidated[28]. The formation of three C—C bonds in a single synthetic operation is demonstrated[29] by the thermal addition of the triene *(53)* at 180 °C to maleic anhydride involving an ene reaction of the intermediate Diels-Alder adduct *(54)*. This simple approach to the cage compound *(55)* illustrates the general potential of combining pericyclic reactions in the synthesis of complex molecules.



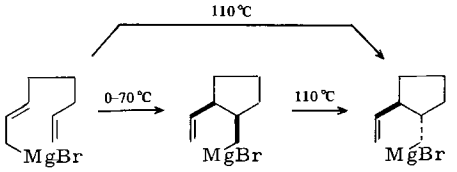
(51) *(52)*



(53) *(54)* *(55)*

Intramolecular ene reactions involving the transfer of atoms other than hydrogen have rarely been observed. An interesting observation[30a,b] is the cyclization of the Grignard reagent

(56) which is readily available in one synthetic operation from butadiene. Even at temperatures between 0 and 70°C, highly selective cyclization to the *cis*-substituted cyclopentane *(57a)* is observed. At 110°C, *(57a)* as well as *(56)* isomerize to the more stable *trans* product *(57b)*, indicating the reversibility of the reaction *(56)* → *(57)* at higher temperatures. Reaction of the cyclic Grignard products *(57)* with a series of electrophiles[30a] provides access to variously functionalized 1,2-disubstituted cyclopentane derivatives in a stereoselective manner.

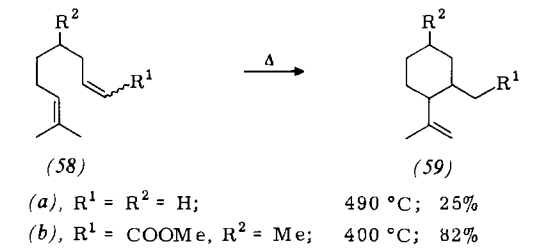


(56) *(57a)* *(57b)*

Analogous lithium transfer seems to occur in the cyclization of 3,7-dimethylocta-1,6-diene with nBuLi/TMEDA to give the allylic carbanion of 1,2-dimethyl-3-isopropenylcyclopentane[30c].

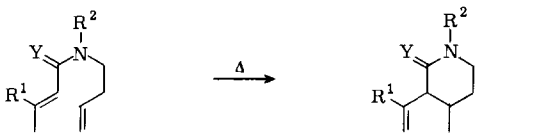
2.2. 1,7-Dienes

1,7-Dienes undergo the intramolecular ene reaction less readily than the corresponding 1,6-dienes. Thus the transformations *(58a)* → *(59a)*[31], *(60a)* → *(61a)*[23,26c] and *(62)* → *(63)*[26a] require higher temperatures and proceed in lower yields. Nevertheless, preparatively useful yields of six-membered ring products such as *(59b)* or *(61b)* may be obtained from 1,7-dienes containing carbonyl-activated enophile or ene components.



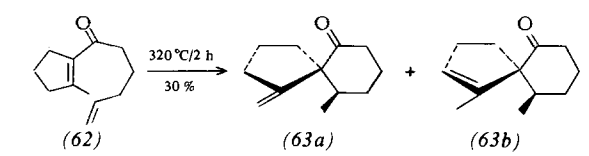
(58) *(59)*

(a), $R^1 = R^2 = H$; 490 °C; 25%
(b), R^1 = COOMe, R^2 = Me; 400 °C; 82%



(60) *(61)*

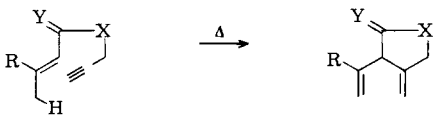
(a), R^1 = H, R^2 = Ac, Y = H_2; 290 °C; 27h; 26%
(b), $R^1 = R^2$ = Me, Y = O; 355 °C; 3h; 65%



(62) *(63a)* *(63b)*

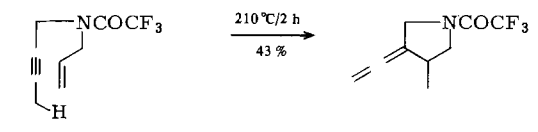
2.3. 1,6-Enynes and 1,2,6-Trienes

In contrast to dienes acetylenes generally participate in intramolecular ene reactions under considerably milder conditions. Thus, even on brief heating at 400°C, the enyne *(64a)* gives the cyclic 1,4-diene *(65a)* in good yield[32]. Cyclization of the enynes *(64b)*[23] and *(64c)*[26c] also proceeds easily at about 200°C to the pyrrolidine derivatives *(65b)* and *(65c)*, respectively, thus demonstrating smooth cyclization of an acetylenic enophile. Alternatively, an acetylenic ene component is involved in the thermal conversion of *(66)* under similar conditions into the allene *(67)*[23]. The quantitative transformation of dehydrolinalool *(68)* into *(69)*[33a] proceeds at 200°C with $\Delta S^{\neq} = -13.7$ cal K^{-1} mol^{-1} and $\Delta H^{\neq} = 28.7$ kcal mol^{-1}[19] (showing a significantly lower free energy of activation than the analogous reaction of linalool *(5)*). The reaction *(68)* → *(69)* has recently been exploited[33b] in the synthesis of the spirosesquiterpene, β-acoratriene *(72)*. The allylic alcohol in *(69)* serves as the reactive site for the introduction of the remaining carbon atoms of *(72)* *via* the intermediates *(70)* and *(71)*. Similar Claisen rearrangement *via* reaction of *(69)* with 1-ethoxy-1-propene provides easy access to the industrially important perfume ingredient *(82)*[33c].

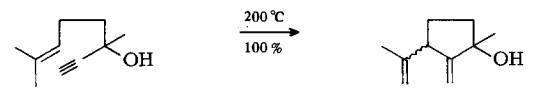


(64) *(65)*

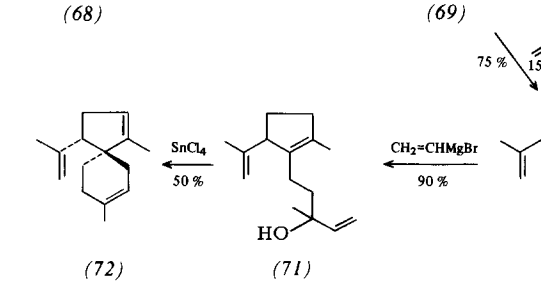
	X	Y	R			
(a),	CH_2	H_2	H	400 °C;	seconds;	65%
(b),	NTs	H_2	H	180 °C;	5h;	50%
(c),	NMe	O	Me	220 °C;	2h;	80%



(66) *(67)*

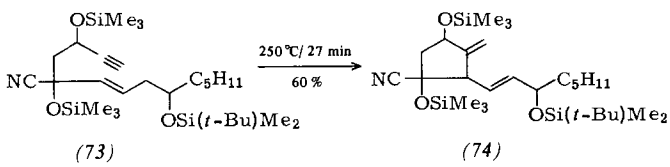


(68) *(69)*



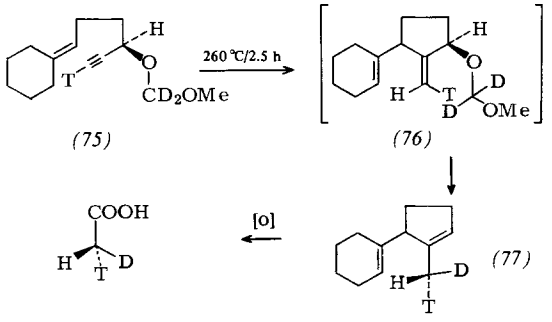
(72) *(71)* *(70)*

Similarly, cyclization of the multifunctionalized enyne *(73)* to *(74)* represents the key step in a total synthesis of prosta-



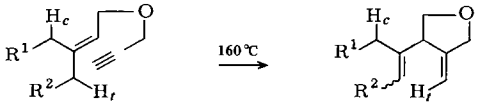
(73) *(74)*

glandins[34]. In an exceedingly elegant synthesis of chiral acetic acid[35], the *supra-supra* character of the ene reaction is utilized in the thermal cyclization of the enyne *(75)* to control the configuration of the exocyclic double bond in the transient product *(76)*. Intramolecular chirality transfer by a subsequent retro-ene reaction, *(76)*→*(77)*, generates the desired asymmetric center. Thus *(77)*, obtained from *(75)* in one synthetic operation, provides after Kuhn-Roth oxidation (*R*)-[^{2}H, ^{3}H]-acetic acid in high optical purity.



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

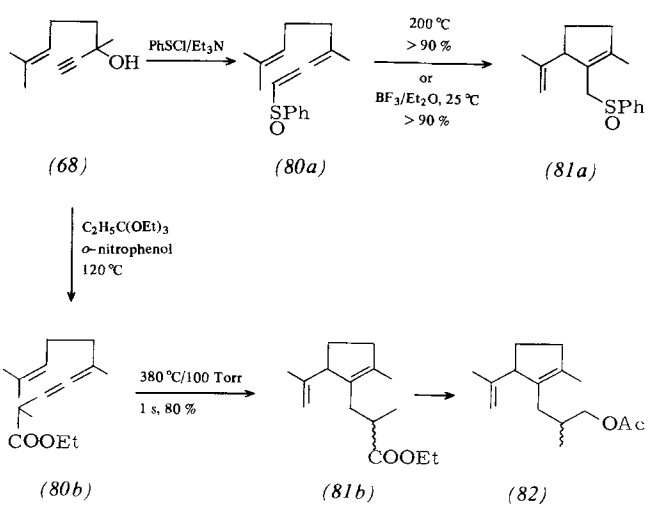
An interesting selectivity is displayed by the thermal cyclizations of the propargyl ethers of nerol *(78a)* and geraniol *(78b)* to *(79a)* and *(79b)*, respectively; in both cases transfer of H_t predominates over H_c-transfer[36a].



(78) *(79)*

(a), R^1 = CH_2–CH=C(CH_3)$_2$, R^2 = H; 85%
(b), R^1 = H, R^2 = CH_2–CH=C(CH_3)$_2$; 75%

Recently, it has been shown[36b] that the sulfoxide *(80a)*, containing an allenic enophile unit, cyclizes quantitatively to the doubly functionalized cyclopentene derivative *(81a)*. Striking rate enhancement of this reaction can be achieved by Lewis acid catalysis. An industrial process, actually carried out on a scale of several 100 kg, involves efficient thermolysis of the allene *(80b)* (also readily prepared from *(68)*) to give *(81b)*, which is then converted into the odorant *(82)* (also accessible from *(69)*, *vide supra*)[36c].



(68) *(80a)* *(81a)*

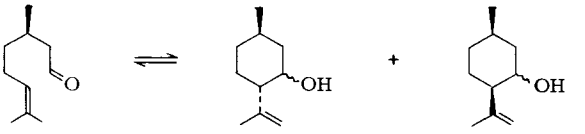
(80b) *(81b)* *(82)*

2.4. Enones

Intramolecular ene reactions of enones have been widely used in the synthesis of five- and six-membered ring systems. The carbonyl group serves either as the enophile or, *via* its enol tautomer, as the ene unit.

2.4.1. Hydrogen Transfer from Carbon to Oxygen (Carbonyl as Enophile)

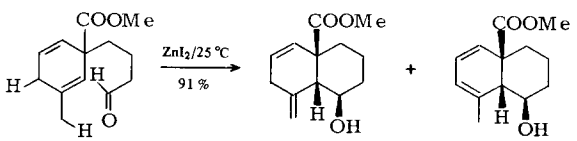
Although the acid-induced cyclization of citronellal *(83)*, observed as long ago as 1896[37], probably proceeds *via* cationic intermediates, the thermal transformation *(83)*→*(84)* at 350 °C, first reported 31 years later[9], may be described by an intramolecular ene mechanism. This mechanism is also implicated in the reverse process, which proceeds at 500 °C and reflects the delicate energy balance between *(83)* and *(84)*. Both the forward[9] and reverse[10] reactions were observed before the ene reaction was formulated as a general reaction principle.



(83) *(84a)* β-OH *(84b)* α-OH *(84c)* β-OH *(84d)* α-OH

180 °C/30h	49%	16%	4%	12%
$ZnBr_2$/5-10 °C/15 min	66%	4%	traces	
[$RhCl(PPh_3)_3$] 25 °C/15h	14%	41%	–	–

Because of its industrial importance the pyrolytic cyclization of citronellal *(83)* has been restudied in more detail[38a–c]. Heating of *(83)* at 180 °C leads to all possible stereoisomeric isopulegols *(84)*, the major isomer *(84a)* exhibiting *trans*-related hydroxyl and isopropenyl groups. This isomer is formed even more selectively from *(83)* at low temperature in the presence of 1 equiv. of $ZnBr_2$[38d]. On the other hand, when the reaction is catalyzed by tris(triphenylphosphane)rhodium chloride, *(84b)* is formed as the predominant isomer at 25 °C[39]. The analogous cyclization of the benzylimine derived from *(83)* in the presence of $SnCl_4$ at −25 °C[40] yields a similar product pattern as the uncatalyzed process of *(83)*. A related example is the synthesis of the eudesmane sesquiterpenes: the aldehyde *(85)*, readily available *via* reductive alkylation of *m*-toluic acid, smoothly isomerizes in the presence of zinc iodide catalyst to a 1:3 mixture of the bicyclic dienols *(86a)* and *(86b)*[41].

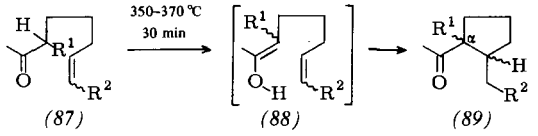


(85) *(86a)* *(86b)*

2.4.2. Hydrogen Transfer from Oxygen to Carbon (Enol as Ene-Component)

Monocyclization: By far the largest number of intramolecular enone cyclizations described to date involve hydrogen

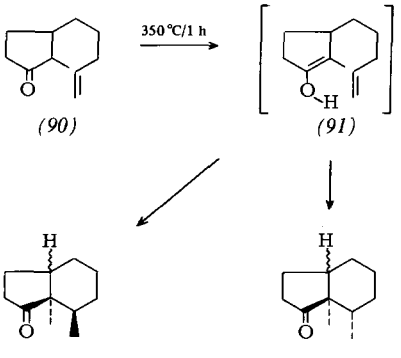
transfer from an enol intermediate to an olefinic enophile. As developed by *Conia et al.*, this method leads to an enormous variety of monocyclic, bicyclic, and bridged systems. A few selected examples will suffice here in order to discuss this principle within the framework of the intramolecular ene reaction (for a major review see [42]). Thus ε,ζ-unsaturated ketones *(87)*, on heating at 350—270°C on a Pyrex surface, furnish substituted cyclopentanes *(89)* in high yield[43]. In general, these reactions proceed by two successive steps: rate-determining tautomerization, *(87)* → *(88)*, followed by the actual cyclization process, *(88)* → *(89)*. The high temperatures and surface catalysis required for the first step somewhat limit the general applicability of this reaction. Subsequent enolization determines also the *trans* configuration of the products *(89a)* and *(89b)* containing available α-hydrogens. However, in analogy to cyclizations of 1,6-dienes, kinetic control favors a *cis* relationship between the hydrogen donor and hydrogen acceptor units in the product, as in *(89c)*.



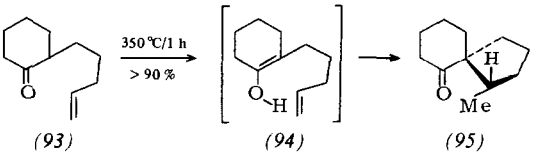
(87) *(88)* *(89)*

(a), $R^1 = R^2 = H$; R^1/H: *trans*; 84%
(b), $R^1 = H$; $R^2 = COOMe$; R^1/H: *trans*; 90%
(c), $R^1 = Me$; $R^2 = H$; R^1/H: *cis*; 90%

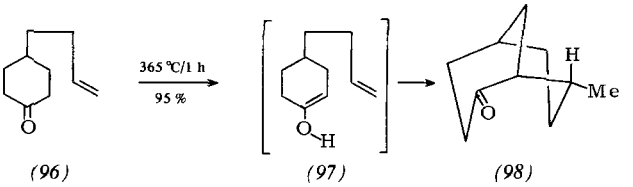
In the kinetically controlled pyrolysis of cyclic ketones the stereochemical outcome depends on whether the enol intermediate is fixed in the *trans* or *cis* configuration with respect to the enophilic bridge. Thus, in accord with model considerations, the "*trans*" enol intermediate *(91)* derived from *(90)* affords[44] a mixture of the stereoisomers *(92a)* and *(92b)*, whereas the *cis* enol *(94)* resulting from *(93)* provides[45] exclusively the spiro product *(95)* with *cis*-related methyl and carbonyl groups. Furthermore, bridged ring systems are easily accessible, as exemplified by the efficient thermal conversion of *(96)* into *(98)*[46].



(90) *(91)* *(92a)* 17% *(92b)* 58%

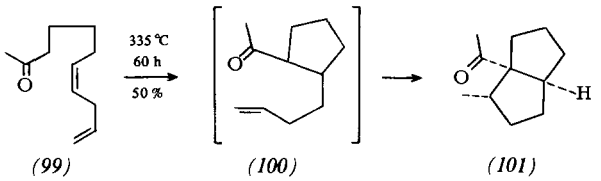


(93) *(94)* *(95)*

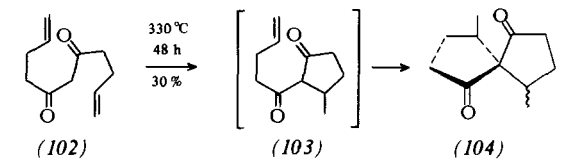


(96) *(97)* *(98)*

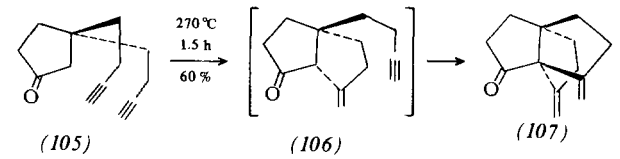
Double cyclizations: Elegant examples exploiting successive pericyclic reactions include the thermal conversions *(99)* → *(101)*[47], *(102)* → *(104)*[47], and *(105)* → *(107)*[48]. Thus a single synthetic operation involving two sequential ene reactions provides fused, spiro, and propellane systems.



(99) *(100)* *(101)*



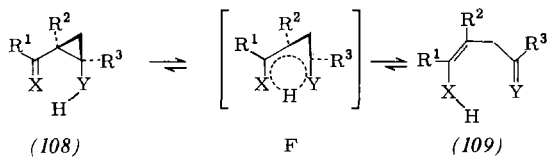
(102) *(103)* *(104)*



(105) *(106)* *(107)*

2.5. Retro-Ene Reactions

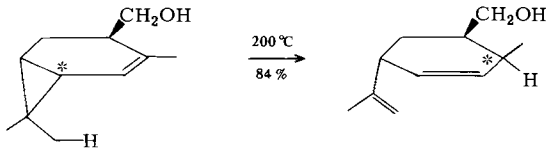
Ring strain effects clearly shift the equilibrium between *(108)* and *(109)* highly in favor of the diene (retro-ene process)[49]. In agreement with a concerted retro-ene mechanism (transition state F), cyclopropanes with *cis*-related hydrogen donor (Y) and acceptor (X) units cleave at significantly lower temperatures than the corresponding *trans* isomers.



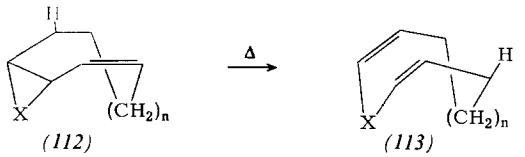
(108) F *(109)*

2.5.1. Hydrogen Transfer from Carbon to Carbon

The suprafacial character of the retro-ene reaction is further demonstrated by the highly specific chirality transfer observed[50] in the conversion of the carene derivative *(110)* into the menthadiene *(111)*. The related ring enlargement reaction of the annelated cyclopropanes[51] and epoxides[52] *(112)* into dienes *(113)* implies transannular hydrogen transfer and concomitant cleavage of the C—C bond common to the two rings.



(110) (111)



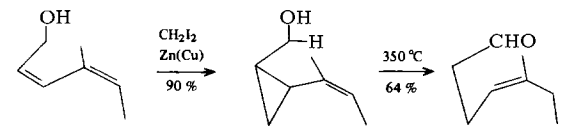
(112) (113)

(a), X = $CHCH_2OH$; n = 2; 340°C; seconds

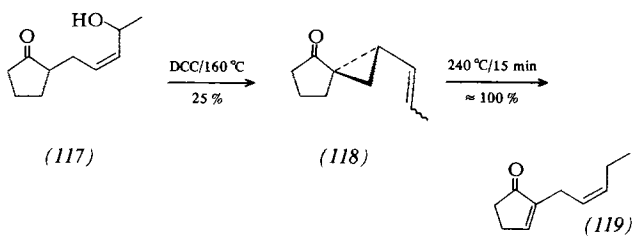
(b), X = O; n = 2; 195°C; 2 days

(c), X = CH_2; n = 1; 180-300°C; ?

The earlier observations concerning the selective formation of (*Z*)-olefins *(109)* in the ring opening of the *cis*-alkylvinyl cyclopropanes *(108)*[49] have been elegantly exploited[53] in the stereoselective synthesis of the trisubstituted olefin *(116)*. This building block for the synthesis of Cecropia juvenile hormone was obtained by pyrolysis of the *cis*-cyclopropane *(115)* which was readily available from the dienol *(114)*.



(114) (115) (116)

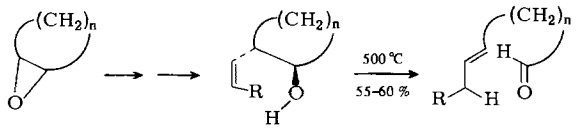


(117) (118) (119)

The synthesis of a jasmone precursor *via* the sequence *(117)*→*(118)*→*(119)* also illustrates the highly stereoselective (Z)-olefin formation in the retro-ene step *(118)*→*(119)*[54].

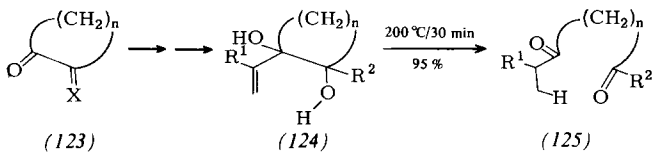
2.5.2. Hydrogen Transfer from Oxygen to Carbon

As mentioned earlier (Section 2.4), the equilibrium *(83)* ⇄ *(84)* is shifted to the side of the acyclic enone *(83)* at higher temperatures. Likewise, unsaturated aldehydes *(122)* with different chain lengths can be obtained by heating the β-hydroxyolefins *(121)* to 500°C[38a, 55a]. For example, *trans*-2-vinylcyclohexanols, prepared by acid treatment of 7-hydroxymethylbicyclo[4.1.0.]heptanes, on heating to 440°C for 2 min afforded stereoselectively (*E*)-ε,ζ-unsaturated carbonyl compounds[55b]. At considerable lower temperature, the unsaturated glycols *(124)* cleave readily to the energetically more favorable diketones *(125)*[56]. Loss of cyclobutane ring strain facilitates the related cleavage of *(126)* to the γ,δ-unsaturated aldehydes *(127)*[57].



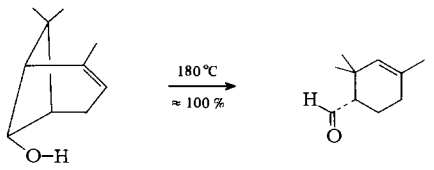
(120) (121) (122)

R = *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}; n = 3, 4, 5



(123) (124) (125)

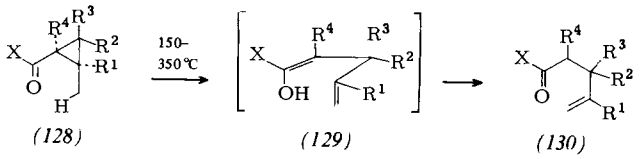
R^1 = H, Me; R^2 = H, Me, Et; n = 3, 10



(126) (127)

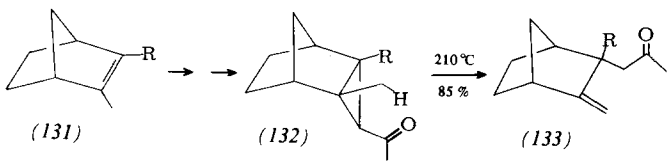
2.5.3. Hydrogen Transfer from Carbon to Oxygen

cis-Methylcyclopropane carbaldehydes, ketones, and esters *(128)* also undergo thermal ring opening to provide γ,δ-unsaturated carbonyl compounds *(130)* in good yields[49a, 49c, 58]. This conversion, proceeding *via* enol *(129)*, as well as the related transformation *(132)*→*(133)*[59], correspond to the retro-ene equivalent of the reaction *(87)*→*(88)*→*(89)* mentioned in Section 2.4.2. The analogous examples *(135)*→*(136)*



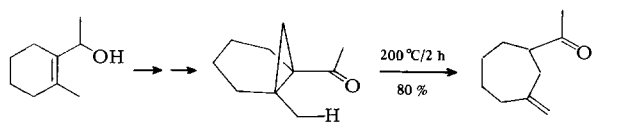
(128) (129) (130)

X = H, Alkyl, Aryl, OMe

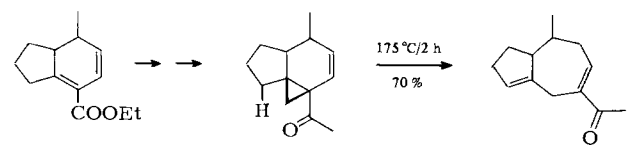


(131) (132) (133)

R = H, Me



(134) (135) (136)



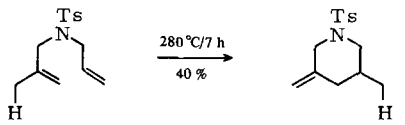
(137) (138) (139)

and *(138)*→ *(139)* represent interesting thermal ring enlargements[60]; thus, the annelated cycloheptane *(139)* is a potential precursor for the synthesis of hydroazulene sesquiterpenes.

3. Type II Additions

3.1. 1,6-Dienes

The Type II addition of dienes has hitherto received relatively little attention. This reaction occurs less readily than the corresponding Type I addition, as seen by the low conversion of *(140)* into *(141)*[61]. Likewise, the thermolysis of



(140) *(141)*

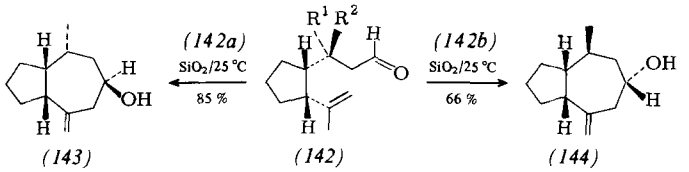
(19), $R^1 = R^3 = Me$, $R^2 = H$, which offers internal competition between Type I [→ *(20)*] and Type II [→ *(21)*] modes also shows high preference for the former process.

3.2. Enones

The preparative utility of the Type II additions of enones can be illustrated with the aid of a few examples.

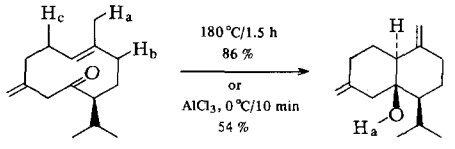
3.2.1. Hydrogen Transfer from Carbon to Oxygen (Carbonyl as Enophile)

Hydroazulene derivatives are formed in high yield by silica gel catalyzed cyclizations of enones *(142a)* and *(142b)*[62]. The operation of an ene process appears to be responsible for the exclusive formation of *exo*-methylene products and for the high stereoselectivity; in both cases major isomers are formed, to which structures *(143)* and *(144)*, respectively, have been assigned[62a, 62b]. This approach to hydroazulenes has been exploited in the synthesis of the sesquiterpene



(143) *(142)* *(144)*

(a), R^1 = Me, R^2 = H; *(b)*, R^1 = H, R^2 = Me

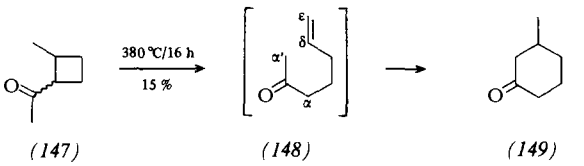


(145) *(146)*

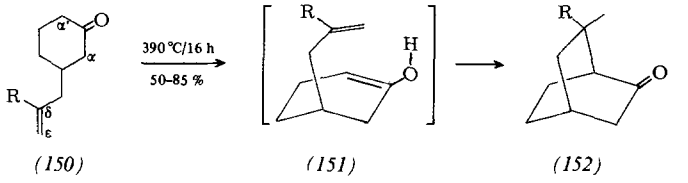
(+)-kessanol[62d]. Recently, the analogous stereoselective cyclization of a δ,ε-unsaturated aldehyde to produce a methylenedecanol was also observed[62e]. In the thermolytic or Lewis acid-catalyzed cyclization of the ten-membered ring enone *(145)* to the decalin *(146)*[63], conformational factors appear to favor transfer of H_a (Type II addition) over transfer of H_b or H_c (Type I addition).

3.2.2. Hydrogen Transfer from Oxygen to Carbon (Enol as Ene Unit)

δ,ε-Unsaturated ketones with available α'-protons form cyclohexanones (Type II) rather than cyclobutyl ketones (Type I) because of ring strain. In fact, retro-ene reaction of *(147)* gives *(148)* which cyclizes *via* its α'-enol directly to *(149)* at higher temperatures[64]. Complicated bridged ring systems are accessible in an analogous manner by thermolysis of δ,ε- and γ,δ-unsaturated cyclic ketones, as shown by the conversions of *(150)* and *(153)* into the bicyclo[2.2.2]octanone *(152)*

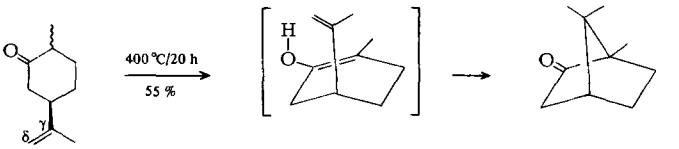


(147) *(148)* *(149)*



(150) *(151)* *(152)*

R = H, Me

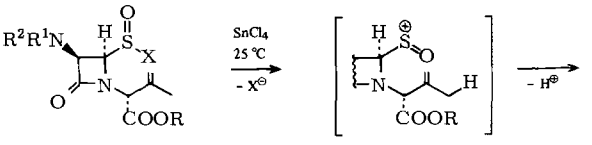


(153) *(154)* *(155)*

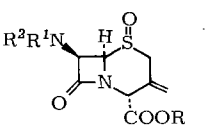
and camphor *(155)* respectively at 400 °C[65]. The relative configuration of *(152)* results from the *endo* transition state requirement in Type II additions.

3.3.3. Sulfinyl Cations and Nitroso Groups as Enophiles

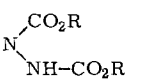
Although groups with hetero multiple bonds such as azo and nitroso groups may serve as effective enophiles in intermolecular ene reactions[7], their participation in intramolecular



(156) *(157)*



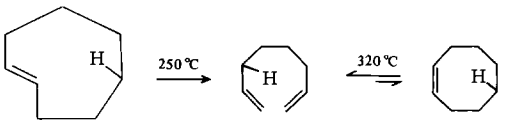
(158)

X = Cl, OH, S-*i*-Pr, NHPh, 

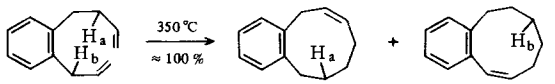
ene processes have rarely been tested. One of the few reports[66] describes the transformation of *(156)* derived from penicillin sulfoxide into the cepham *(158)*, presumably *via* the transient sulfinium ion *(157)*. An analogous cyclization of an unisolable aliphatic nitroso compound into a cyclic hydroxylamine has been described[67].

4. Type III Additions

The few cases of Type III reactions so far reported deal with the thermal equilibrium between medium-sized cycloalkenes and acyclic α,ω-dienes, the latter being favored at higher temperatures[7, 49a, 68]. For example, 1,7-octadiene *(160)* is obtained on heating *trans-* *(159)* or *cis*-cyclooctene *(161)*,



(159) *(160)* *(161)*



(162) *(163)* *(164)*

the more strained *trans*-isomer opening at lower temperature. In contrast, exclusive cyclization, *(162)* → *(163)* + *(164)*, was observed at 350 °C[69].

5. Discussion

The available evidence allows the following generalizations.

5.1. Entropic Assistance

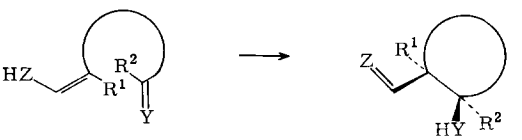
Since the intermolecular ene process shows a high negative entropy of activation[2b, 7] it clearly should profit from intramolecularity, as is well known for other pericyclic reactions[14]. Accordingly, kinetic measurements of the transformations *(1)* → *(2)* and *(5)* → *(8)* + *(9)* show an activation enthalpy $\Delta H^{\neq} = 31.2$ to 31.8 kcal mol^{-1} and an activation entropy $\Delta S^{\neq} = -18.0$ to -19.4 cal K^{-1} mol^{-1}, whereas the intermolecular ene reactions of alkenes with maleic anhydride exhibit activation parameters $\Delta H^{\neq} = 18.0$ to 21.5 kcal/mol and $\Delta S^{\neq} = -36$ to -45 cal K^{-1} mol^{-1}[2b]. It thus appears that the effective participation of nonactivated enophiles in the intramolecular ene process is due to the less negative $\Delta S^{\neq}$ which compensates for the higher $\Delta H^{\neq}$ values. Intramolecularity also facilitates the ene reactions of activated enophiles as exemplified by the reactions *(30)* → *(31)* and *(51)* → *(52)*.

5.2. Direction of Addition

In 1,6- and 1,7-dienes and -enynes and the corresponding enones and dienols containing several allylic or propargylic hydrogens, preference for hydrogen transfer follows the order Type I > Type II > Type III [for an exception see the reaction *(145)* → *(146)*]. When the linking chain is shorter than three atoms, formation of three- to four-membered rings by the Type I pathway is thermodynamically disfavored thereby promoting the less strained Type II products, as illustrated by the transformations *(147)* → *(148)* → *(149)*, *(150)* → *(152)* and *(153)* → *(155)*. In most reactions of Type I and Type II, carbon-carbon bond formation occurs preferentially between the closest unsaturated centers. This preference, observed in the formation of five-, six- and seven-membered rings using nonpolarized enophiles may be ascribed to entropic factors consistent with an "unsymmetrical" transition state[3]. Thus, the development of the C—C-bond being more advanced in the transition state than H-transfer concords well with the regioselectivity which is also observed for other biradicaloid intramolecular processes. Steric repulsion probably favors C—C bond formation between terminal olefinic centers in Type III additions of α,ω-dienes to give medium-sized rings.

5.3. Stereochemistry

In systems where the ene and the enophile units are linked by three or four atoms, the highly ordered transition state may induce useful *endo-exo* discrimination avoiding nonbonding interactions between the bridge and substituents and/or bond angle deformation. For example, the Type I additions of systems containing the hydrogen donor site Z *cis* with respect to the enophilic chain (Scheme 4) exclusively lead to rings where the H-donor and H-acceptor sites Z and Y appear in a *cis* relationship, *e.g. (18)* → *(20a)*, *(23)* → *(24)*, *(38)* → *(39)*, *(94)* → *(95)*. Model considerations clearly show this selectivity to be derived from a strong preference for the *endo* over the *exo* transition state which would exhibit considerable angle strain (see also Scheme 3).



Scheme 4. Stereochemistry of Type I reactions involving "*cis*" enophiles.

For the same reason, Type II reactions can occur only in an *endo* manner when leading to five-, six- or seven-membered rings [see *e.g. (150)* → *(151)* → *(152)*]. The counterplay of kinetic *versus* thermodynamic control may influence the stereochemical outcome as seen in the thermolysis of *(5)*, *(25)* and *(56)*.

6. Concluding Remarks

Accumulating evidence points to the synthetic potential of the intramolecular ene reaction. Based on the given examples a set of rules have been derived, similar to those obtained for intramolecular cycloaddition reactions[14]. Particular mention should be made of the stereoselective construction of five-membered carbo- and heterocyclic systems including substituted, annelated, spiro-fused and bridged systems. The smooth intramolecular ene reaction involving magnesium transfer merits further application and suggests the use of other organometallic ene components. More attention could also be given to the Type II process using activated enophiles. Combination of an intramolecular ene process either with itself or with other pericyclic reactions offers additional fascinating possibilities. It appears possible that further mechanistic details of the ene reaction may be revealed through work on the intramolecular variant. In view of the continuing need for high yield and selective carbon-carbon bond forming cyclizations in the synthesis of natural products and other complex

molecules, further exploitation of this reaction is expected in the near future.

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Organic Reactions at Alumina Surfaces

By Gary H. Posner[*]

New synthetic methods (24)

Recent examples are given to emphasize that alumina can cause many different and often unexpected chemical reactions of adsorbed organic molecules. Recent developments are summarized to publicize that reagent-doped alumina can be used deliberately to achieve some very mild and highly selective organic transformations. The scope and limitations of organic reactions at alumina surfaces are discussed, and the advantages of these heterogeneous reactions over the corresponding homogeneous ones are pointed out. The role of the alumina and future problems are discussed briefly.

1. Introduction

The main purpose of this article is two-fold: (a) to emphasize with recent examples the pronounced catalytic activity of γ-alumina in causing various adsorbed organic molecules to undergo many different types of often unanticipated chemical reactions[1] and (b) especially to publicize recent developments involving *deliberate* placement of different reagents on solid alumina and use of this doped alumina to cause diverse organic reactions heterogeneously at the alumina surfaces under unusually mild conditions. The examples given in the article were chosen to illustrate the most important results for organic synthesis, and they do not represent all literature reports on this subject. The nature of γ-alumina has been reviewed[2], and therefore it will not be discussed here at length; catalytically active γ-alumina as used for chromatography has both acidic and basic sites, and probably the synergistic effect of these two properties on organic molecules is the basis for the unusual mildness and selectivity of many of the chemical transformations discussed in the following sections.

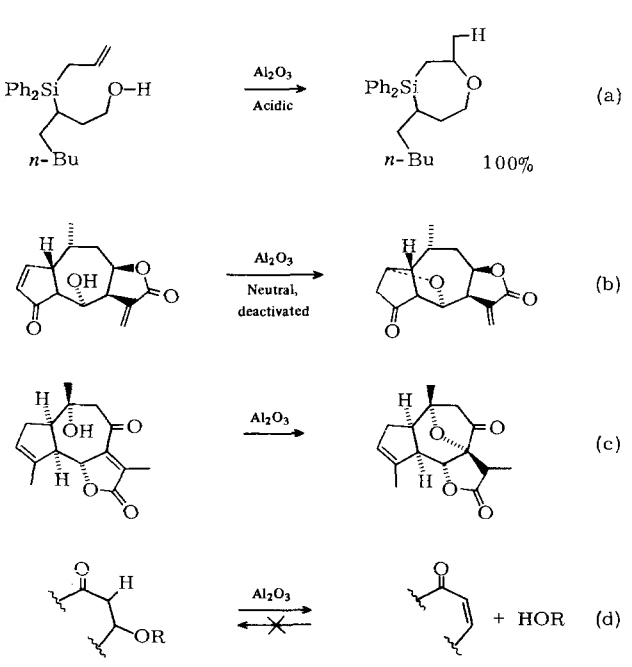
Although a 1924 patent reported use of chemical reagents on porous carriers to achieve some highly selective and mild chemical operations[3], not until recently has interest been rekindled in this area, as shown by the dates of the following references: *Collins'* reagent[4] and silver carbonate[5] on Celite, chromic acid on an anion exchange resin[6] and intercalated in graphite[7], and chromyl chloride on silica-alumina[8] for alcohol oxidations; ozone on silica gel for oxidation of tertiary alkyl centers[9], for oxidation of arenes[10] and for oxidation of primary amines to their nitro derivatives[11]; thallium trinitrate on K-10 montmorillonite clay for oxythallation reactions[12]; alcohols on various zeolites[13] for reduction of small carbonyl compounds[14]; nitric acid on Celite for aromatic nitration[15], and $SbCl_5$ intercalated in graphite for substitution of bromine by chlorine[16,17].

These heterogeneous organic reactions effected by reagents immobilized on porous solids are becoming very useful to chemists involved with laboratory-scale synthesis mainly for the following reasons: (a) they are often more selective than the corresponding homogeneous reactions, and therefore some heretofore impossible transformations are made possible; (b) they are usually milder than the corresponding homogeneous reactions thus allowing some highly sensitive molecules to be used as reactants; and (c) they are often operationally simpler to perform than the corresponding homogeneous reactions, with product isolation usually involving only filtration and solvent evaporation. Organic reactions at *alumina* surfaces also usually possess advantages (a)—(c).

2. Addition Reactions

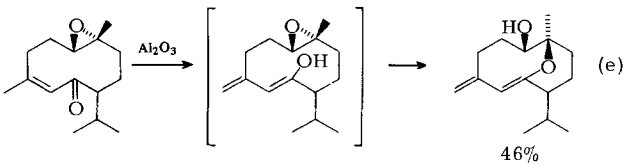
2.1. Intramolecular Addition of O—H Groups

Alumina-induced intramolecular additions of hydroxyl groups across isolated [eq. (a)][18,21] and carbonyl-conjugated [eq. (b) and (c)][19,20] carbon-carbon double bonds have been reported. Intramolecularity is a critical feature of these reactions because no comparable alumina-promoted intermolecular additions of alcohols to alkenes or of alcohols to α,β-unsaturated carbonyl compounds have been observed. In contrast to this intramolecular OH *addition*, alumina in fact has been used to produce α,β-ethylenic ketones *via elimination* of alcohols from β-alkoxyketones [eq. (d); cf. Section 5.2].



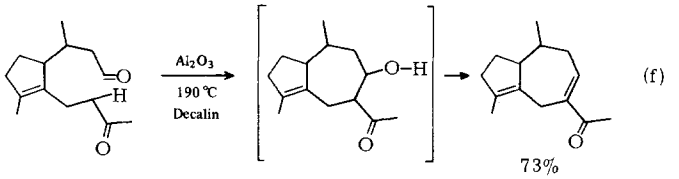
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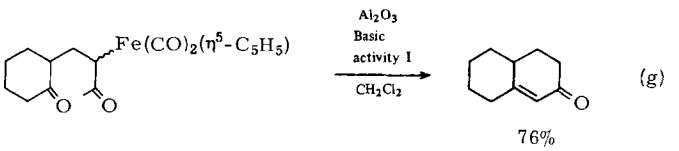
An unusual example has been published dealing with alumina-promoted ketone enolization and subsequent intramolecular addition of the enolic OH group across a transannular epoxide [eq. (e)][22].

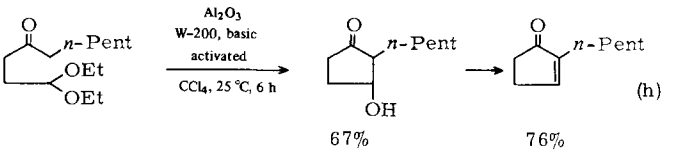


2.2. Intramolecular Addition of Acidic CH Groups

As shown in eq. (e), some forms of alumina are sufficiently basic to cause enolization of ketones. When a second carbonyl group is present in the same molecule, intramolecular addition of the carbon atom of the enol (or the enolate ion) to the nonenolized carbonyl group leads to a carbocyclization reaction. Equations (f) to (h)[23–25] illustrate application of this type of alumina-promoted intramolecular aldol condensation to mild and efficient construction of seven-, six-, and five-membered carbocycles.



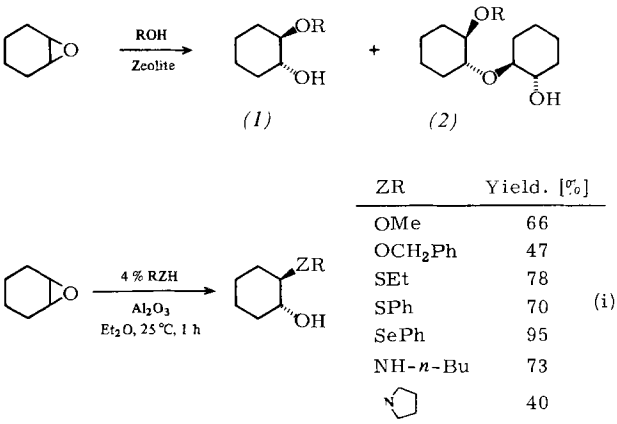




2.3. Intermolecular Addition of OH and other Heteroatom-H Groups

Despite the sporadic reports of alumina catalyzing intramolecular addition of O—H groups, prior to 1974 no one had intentionally added an alcohol and an electrophile to alumina. In 1974, we began a systematic study aimed at using porous chromatographic alumina as a catalyst for intermolecular nucleophilic addition of various heteroatom-H (RZ-H) species to electrophiles. Of the electrophiles examined (olefins, ketones, epoxides), epoxides were the most promising. We have found that a stirred slurry of commercially available[26] Woelm, 200, neutral (W-200-N) chromatographic alumina (activity "super I" on the Brockmann scale)[27] catalyzes opening of a very wide variety of epoxides by only a few equivalents of RZ-H nucleophiles reproducibly and under exceedingly mild conditions (10 min to 1 h, 25 °C, diethyl ether solvent)[28]. Although our initial work was done with W-200-N alumina which we had activated at 400 °C under vacuum[29], we have recently found that W-200-N alumina used directly from the commercial can gives essentially the same results. Nucleophiles successfully incorporated under these conditions include alcohols, thiols, benzene selenol, amines, and acetic acid. Alumina impregnated with a few equivalents of these nucleophiles opens epoxides regioselectively at the less substituted epoxide carbon atom and stereospecifically *(trans)* to give the corresponding β-functionalized alcohols cleanly and in good yields[28].

Reactions of epoxides with active chromatographic alumina has been reported to give usually a mixture of products containing mainly allylic alcohols[30]. An aluminosilicate molecular sieve (zeolite) has recently been used for catalytic alcoholysis of cyclohexene oxide, giving a mixture of 1,2-cyclohexanediol derivative *(1)* and dicyclohexyl ether *(2)*[31]. In contrast, cyclohexene oxide reacts with Woelm-200-N alumina carrying 4 % of RZ-H to give the corresponding *trans*-2-functionalized cyclohexanols reproducibly in good yield as the only product [eq. (i)]. No allylic alcohol, 1,2-diol, or *cis*-isomer was detected. Several grams of epoxide have been successfully opened by this heterogeneous reaction on RZ-H doped alumina[28]. The yields given in eq. (i) refer to purified products.

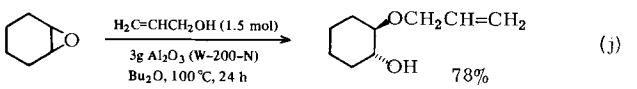


ZR	Yield. [%]
OMe	66
OCH_2Ph	47
SEt	78
SPh	70
SePh	95
NH-*n*-Bu	73
	40

(i)

In several cases cyclohexene oxide reactions with RZ-H-doped alumina are superior to homogeneous methods for synthesis of the corresponding 2-RZ-cyclohexanols[28].

Typically, about 7.5 g of the W-200-N alumina per 1 mmol of epoxide is required for complete reaction at 25 °C. By operating with dibutyl ether as solvent at 100 °C for 24 h, however, we have recently been able to use only 3 g of W-200-N alumina to convert 30 g (≈ 300 mmol) of cyclohexene oxide [eq. (j)][32]. This type of *catalytic* reaction is very appealing for possible application to large-scale reactions.



30g (0.3 mol)

The oxides of symmetrical 5-, 7-, 8-, and 12-membered cycloalkenes also undergo mild and selective opening by RZ-H doped alumina[28].

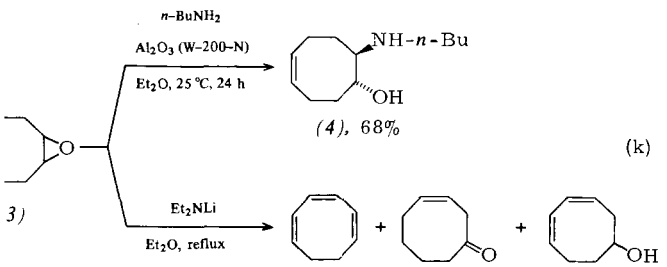
Medium ring (C_8—C_{12}) cycloalkene oxides are much less reactive than cyclohexene oxides and are difficult to open homogeneously to only 2-functionalized cycloalkanols; direct

1,2-epoxide opening is usually accompanied by substantial amounts of side products derived from transannular interactions[33]. In sharp contrast to these homogeneous reactions, *no* products arising from transannular interactions were found in the RZ-H-doped alumina catalyzed opening of these medium ring cycloalkene oxides, and the yields of pure 1,2-opened products were reproducibly good. This mild and clean heterogeneous opening of medium ring epoxides by RZ-H-impregnated alumina appears to be the best method for stereospecific conversion of medium ring *cis*- or *trans*-cycloalkene oxides into the corresponding *trans*- or *cis*-2-substituted cycloalkanols, respectively.

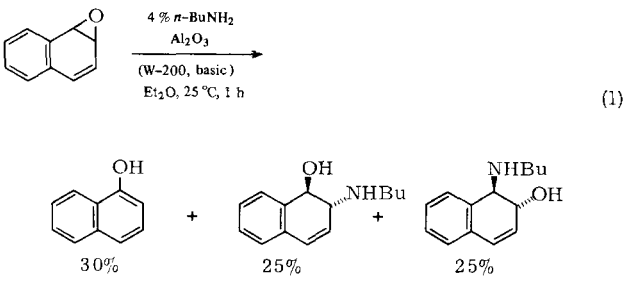
Oxides of symmetrical acyclic alkenes (symmetrically substituted oxiranes) also undergo clean nucleophilic *trans*-opening with RZ-H species on alumina, and unsymmetrically substituted oxiranes are cleaved with preferential attachment of the RZ unit at the less substituted epoxide carbon atom. For example, a regioselectivity of 6:1 was observed for an unsubstituted *versus* a mono- or di-substituted epoxide carbon atom on reaction with ROH on alumina[28].

Because it is often desirable to open an epoxide in the presence of some other functional group (*i. e.* chemoselectively), we have established that alcohols, nitriles, ketones, esters, and olefins are relatively stable to RZ-H-doped alumina for one hour at 25 °C[28].

1,5-Cyclooctadiene monoxide *(3)* has been reported to react with lithium diethylamide to give a mixture of cyclooctene derivatives [eq. (k)][34]. In contrast, *n*-butylamine-doped alumina produced analytically pure *trans*-amino alcohol *(4)* in 68% yield after column chromatographic purification. Likewise, in sharp contrast to homogeneous acidic solvolysis of the epoxide *(3)*, which gave bicyclic products in 20% yield, acetic acid-doped alumina gave no bicyclic products. These results and particularly those with epoxycyclooctane support the notion that nucleophilic opening of epoxides by RZ-H-doped alumina is a concerted and not a stepwise process[28].



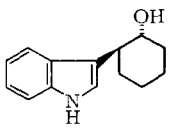
RZ-H-doped alumina also catalyzes *trans*-opening of vinyl- and aryloxiranes, and of both K-region and non-K-region arene oxides[35]. Vinyloxiranes, such as 1,3-cyclopentadiene monoxide, undergo regiospecific attack by RZ-H species at the allylic carbon-oxygen bond to form homoallylic alcohols. Indene 2,3-oxide reacts with methanol-doped alumina to give *trans*-1-methoxy-2-indanol exclusively in 97% yield, with complete regiospecificity and stereospecificity. Amine-doped alumina is the only method now available for opening naphthalene 1,2-oxide (and probably other non-K-region arene oxides) by weak nitrogen nucleophiles [eq. (l)]. This result is especially significant because opening of arene oxides by weak nucleophiles is considered such a fundamental step in the expression of the toxicological effects of these systems[35].



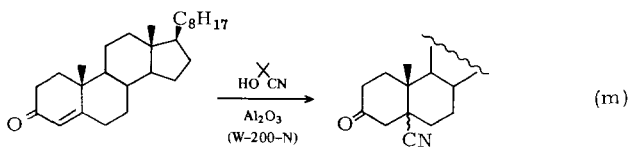
These epoxide openings effected by alcohols, thiols, benzeneselenol, amines, and acetic acid on commercial W-200-N alumina constitute a useful new synthetic method. This new procedure is characterized by its clean formation usually of only one product, by its practical aspects (direct use of commercially available alumina, room temperature conditions, multi-gram scale reactions, easy product isolation), by its high chemoselectivity, and by its stereospecificity.

2.4. Intermolecular Additions of Acidic C—H Groups

Attempts to form carbon-carbon bonds by placing cyclohexene oxide and 1-octyne, diethyl malonate, or nitromethane on alumina failed to produce any products derived from incorporation of the acidic doping agent[36]. We have two preliminary results, however, which are very encouraging. First, indole-doped alumina cleaved cyclohexene oxide after 10 min at 25 °C with formation of 2-(3-indolyl)cyclohexanol *(5)* in good yield[36]. Secondly, acetone cyanohydrin-doped alumina transferred the nitrile group in a conjugate fashion to carbon-5 of 4-cholesten-3-one [eq. (m)][37]. Further work along these lines may lead to a generally useful method for selective carbon-carbon bond forming reactions at alumina surfaces.



(5)



(m)

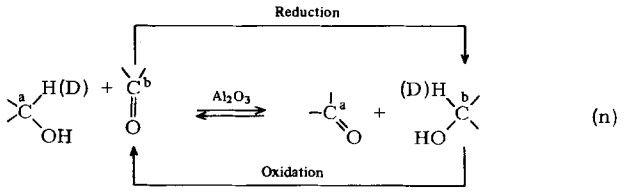
Addition of alumina-generated dihalocarbenes to olefins has been suggested as a simple and convenient method for preparation of dihalocyclopropanes[38].

3. Reduction-Oxidation Reactions

3.1. Reductions

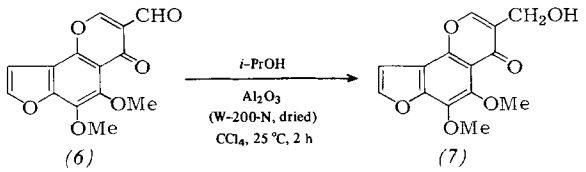
Alumina supporting various metals has been used as an hydrogenation catalyst for reduction of carbon-carbon double bonds[39], and sodium tetrahydridoborate impregnated on neutral alumina has been applied to reduction of carbon-oxygen double bonds especially in base-sensitive molecules[40]. A Cannizzaro-type disproportionation of an aldehyde into the corresponding alcohol and carboxylic acid has been

reported to occur at room temperature over Woelm-I-neutral alumina[41]. Carbonyl addition of a hydride ion derived from a secondary hydroxyl group has been found to occur over alumina *intra*molecularly[42] in the case of some keto alcohols and *inter*molecularly when both alcohol and carbonyl compound are present[43]. That this carbonyl reduction involves hydride (rather than, for example, hydrogen atom) transfer has been established by use of deuterium labeled compounds[44] and by use of cyclobutanol as the hydride donor [eq. (n)][45].



(n)

This Meerwein-Ponndorf-Verley (aluminum triisopropoxide) type carbonyl reduction at room temperature using 2-propanol over W-200-N vacuum-dehydrated alumina has been suggested as a general synthetic method[43a]. The most noteworthy features of this new heterogeneous procedure are as follows: 1) α,β-unsaturated aldehydes can be reduced cleanly to the corresponding allylic (*i.e.*, not saturated) alcohols; 2) aldehydes can be reduced even in the presence of some ketones; 3) many normally labile functional groups (*e.g.* nitro, alkoxycarbonyl, cyano, bromo, and iodo substituents) survive this alumina-based reduction method; and 4) the 2-propanol-alumina "reagent" can be stored in a sealed vial for at least eight months without loss of reducing activity. 2-Propanol on activated Woelm alumina is a reducing "reagent" with selectivity comparable to, or in some cases even greater than,



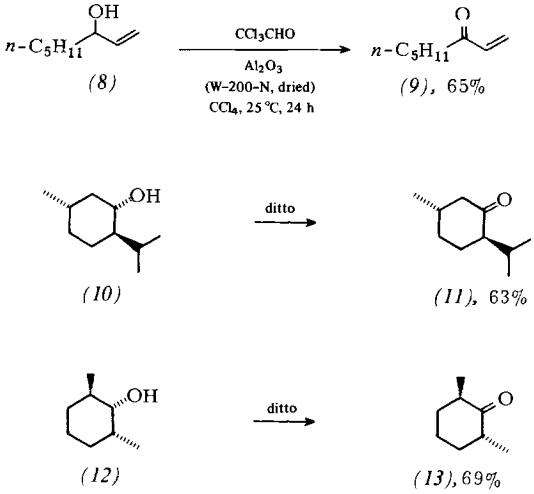
(6) (7)

that of the most sophisticated complex boron and aluminum hydride reducing agents[43a]. For example, chromone *(6)* suffered reduction of both the aldehyde group and the α,β double bond with the following reagents: $NaBH_4$, $NaBH_4/AlCl_3$, diisobutylaluminum hydride in tetrahydrofuran, and $NaB(CN)H_3$ in the presence of acid[43a]. Although polyfunctional chromone *(6)* was inert to aluminum triisopropoxide under homogeneous conditions, selective and effective aldehyde reduction occurred heterogeneously with 2-propanol on activated alumina to give allylic alcohol *(7)* in 80% crude yield (spectroscopically pure) and 55% yield of analytically pure material.

3.2. Oxidations

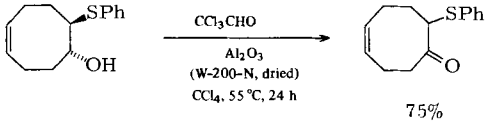
Room-temperature Oppenauer-type oxidation of secondary alcohols to ketones using trichloroacetaldehyde on activated Woelm alumina has also been suggested as a new synthetic method[46]. The most useful aspects of this heterogeneous procedure are its mildness, its tolerance of acid and base sensitive functional groups, and its chemospecificity.

The mildness of chloral on activated Woelm-200-Neutral alumina is illustrated by: (a) oxidation of allylic alcohol *(8)* into vinyl ketone *(9)* which usually polymerizes at the slightest provocation; (b) oxidation of substituted cyclohexanols *(10)* and *(12)* to ketones *(11)* and *(13)* without epimerization to the thermodynamically more stable isomers; and (c) high-yield oxidation of cyclobutanol to cyclobutanone, which process is often accompanied by fragmentation[46b].



Such functional groups as primary iodides, benzylic chlorides, methyl esters, nitro groups, lactones and ethers survive this heterogeneous oxidation procedure[46a].

The chemospecificity of chloral on alumina is illustrated by: (a) oxidation of secondary but not primary alcohols; (b) oxidation of olefinic alcohols to the corresponding olefinic ketones; and (c) oxidation of β-hydroxy sulfides and selenides to the corresponding β-keto sulfides and selenides [*e.g.*, eq. (o)][46b]. Few other homogeneous reagents match this chemospecificity of chloral on activated alumina.



(o)

In contrast to the good reproducibility of all the alumina-based reactions on Woelm alumina discussed in this article, we have found that, contrary to our initially reported data, steroidal diol oxidation gives variable results[46c].

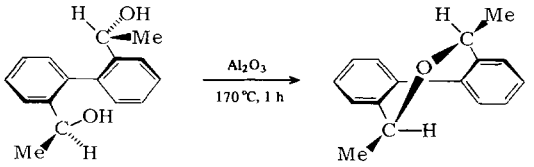
The main disadvantage of chloral on activated alumina for alcohol oxidation is the tediousness of the 400 °C vacuum-drying of the commercial alumina immediately before use. Use of W-200-N alumina without activation, however, led to much inferior results.

4. Substitution Reactions

4.1. Intramolecular Substitution by Heteroatom Nucleophiles

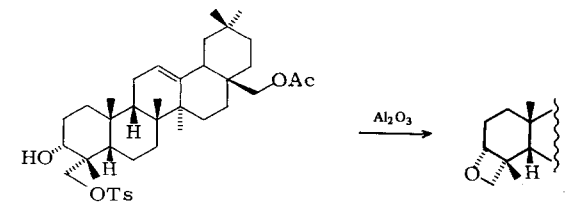
Kessler[47] reported that alumina promoted a stereoselective and concerted (*i.e.*, not ionic) intramolecular substitution of one OH group by a second OH group in the same molecule [eq. (p)]; it was suggested that the role of the alumina was

to facilitate removal of the first OH group as the new ether linkage was being formed.

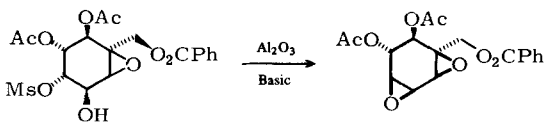


(p)

Intramolecular displacement of sulfonate groups by neighboring hydroxyl groups has also been reported, leading to four-membered (oxetane)[48] and three-membered (oxirane)[49] oxygen heterocycles [eq. (q) and (r)].

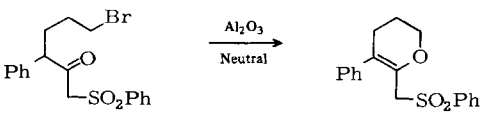


(q)



(r)

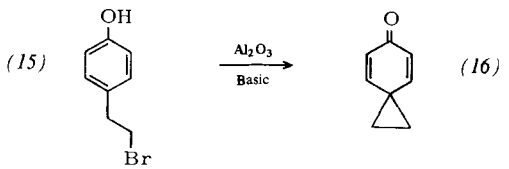
Cook and *Magnus*[50] showed that bromo ketone *(14)* was enolized by alumina and that intramolecular substitution of bromine took place exclusively with the enolic oxygen as nucleophile; no enolic *C*-alkylation occurred.



(14) 95%

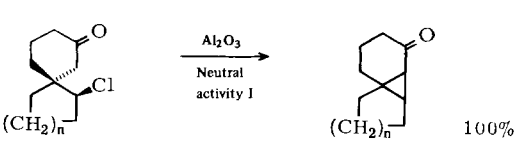
4.2. Intramolecular Substitution by Nucleophilic Carbon Atoms

Baird and *Winstein*[51] showed that the unusually reactive spiro-dienone *(16)* was best prepared (albeit in low yield) by alumina-promoted intramolecular displacement of bromide ion from 4-(bromoethyl)phenol *(15)*.



(15) *(16)*

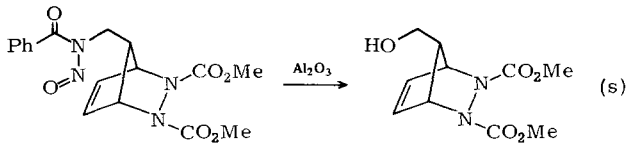
Ruppert and White[52] reported that the facile displacement of chloride ion from chloro ketones *(17)* was due to the stereoelectronically favorable relationship of the leaving group and the alumina-generated neighboring enolate ion.



(17), n = 1,2 100%

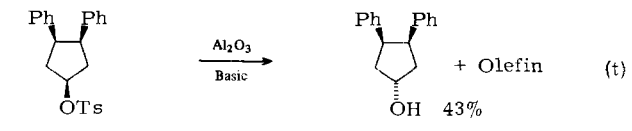
4.3. Intermolecular Substitution by Heteroatom Nucleophiles

Undesired reactions often occur during attempts to purify organic compounds by alumina chromatography[1]. Hydrolysis, for example, involves cleavage of the organic substance by nucleophilic hydroxyl groups on the alumina surface. Historically such alumina-promoted hydrolyses were considered undesirable and unintentional side-reactions; a recent example of an unexpected and unwanted hydrolysis is shown in eq. (s)[53].

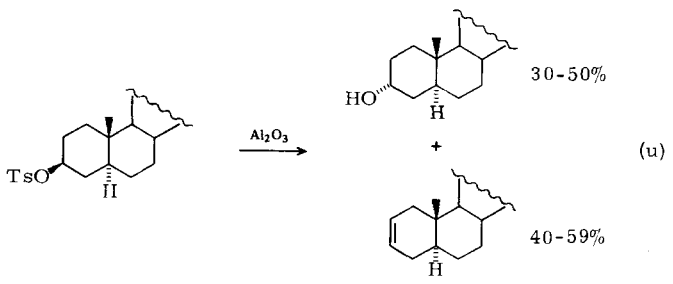


(s)

Recently, however, alumina has been used *intentionally* for mild and selective hydrolysis of some organic molecules. *Johns* and *Jerina*[54] reported that steroidal primary acetates are selectively hydrolyzed on alumina, and *Barton* and coworkers[55] noted that enimides are conveniently hydrolyzed on alumina into enamides. Because carboxylate[56] and sulfonate ester hydrolyses on alumina have been shown to involve *O*-alkyl (rather than *O*-acyl or *O*-sulfonyl) cleavage, hydrolytic epimerization of alcohol derivatives on alumina has been used as a synthetic method in some cases [*e.g.*, eq. (t)[57] and (u)[58]]. The main synthetic limitation to this method, however, is the substantial amount of elimination (*i.e.*, olefin formation) concurrent with hydrolysis (cf. Section 5.3).

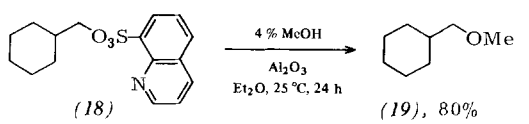


(t)



(u)

In the 1960's *Hodosan* and co-workers reported the first rational attempts to impregnate alumina with heteroatom nucleophiles and to use the doped-alumina for intermolecular substitution of some steroidal tosylates with stereochemical inversion of configuration. Steroidal nitrates, thiocyanates, and isothiocyanates were prepared[59]. More recently we showed that methanol-doped alumina converted L-1-methylheptyl tosylate into D-2-methoxyoctane (40 % chemical yield, 90—95 % net inversion of configuration) and converted the sulfonate ester *(18)* into methyl ether *(19)*[60].



(18) *(19)*, 80%

In 1974, *Hudlicky*[61] reported that a column of acidic alumina "soaked with a solution of benzyl chloride in chloroform containing hydrazoic acid" gave benzyl azide in good yield and under conditions substantially milder than those required in typical homogeneous reactions. We have observed similar substitution reactions of aliphatic and benzylic halides by amine-doped alumina [*e.g.*, eq. (v)][36b].

$$\underset{(1\ \text{Equiv.})}{PhCH_2Cl} \xrightarrow[Et_2O,\ 25\,^\circ C,\ 48\ h]{PhNH_2\ (3\ \text{equiv.}),\ Al_2O_3\ \text{neutral}} \underset{75\%}{PhCH_2NHPh} \qquad (v)$$

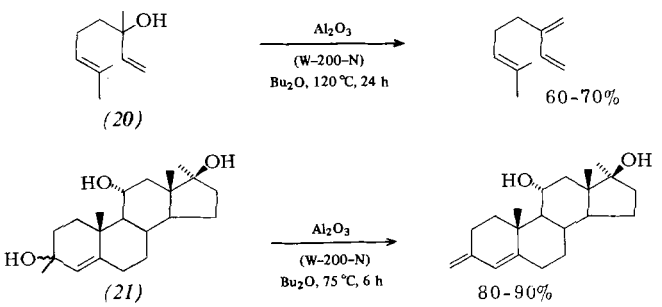
Radical substitution of H by Cl has been reported to occur selectively at the ω-position of octanoic acid adsorbed on neutral alumina[62].

5. Elimination Reactions

This section deals with alumina-promoted elimination of the following groups: H—OH, H—OR, H—OAc, H—OTs, H—halogen, and H—SO_2R.

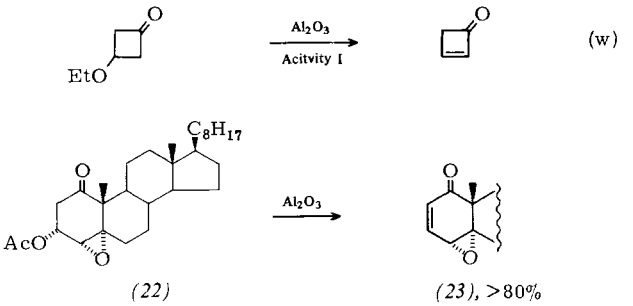
5.1. Elimination of H—OH from Alcohols

Pines and co-workers[63] have studied extensively alumina-induced gas phase dehydration reactions of many small alcohols containing less than 15 carbon atoms, and they have concluded that a carbonium ion mechanism seems to be followed in tertiary alcohol dehydration whereas a synchronous mechanism appears to be operative for secondary and primary alcohol dehydration. *Knözinger* has recently reviewed this subject[64], and two recent articles emphasize that non-Saytzeff elimination often predominates[65]. In 1961, *von Rudloff*[66] reported using alumina doped with pyridine or quinoline to effect dehydration of non-volatile terpene alcohols at ≥200 °C in the liquid phase. Although these conditions have been used in the synthesis of several different sesquiterpene natural products[67], they are not mild and they do not allow selective elimination of one alcohol group in a diol. We have found that linalool *(20)* and the steroidal triol *(21)* undergo mild, selective dehydration when heated in dibutyl ether solvent over commercial W-200-N alumina at 75—120 °C[68].



5.2. Elimination of H—OR and H—O_2CCH_3 from Ethers and Acetates

Ethers and carboxylate esters are normally stable toward alumina at room temperature. When the ether or carbonyl group is located β to a keto group, however, loss of H—OR or of HOAc to form an enone can occur even on alumina chromatography [*e.g.*, eq. (w)][69, 70]. Functionalized steroidal β-acetoxyketone *(22)* reacted chemospecifically on alumina to form epoxy conjugated enone *(23)*[71].



5.3. Elimination of H—OTs from Tosylates

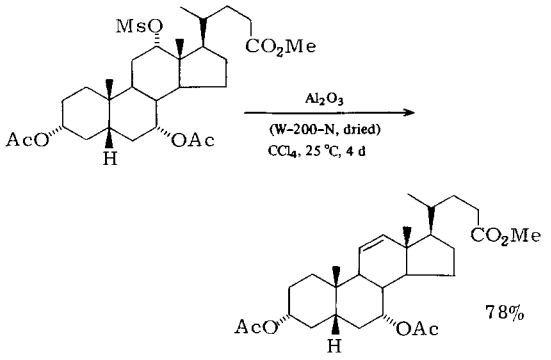
Over the years, various researchers have noticed that alumina chromatography of steroidal sulfonates causes some elimination of the elements of H—OSO_2R to form steroidal olefins as well as some hydrolysis to form epimeric steroidal alcohols (cf. Section 4.3)[72, 73]. Because the hydroxyl groups on the alumina surface were the cause of the competing hydrolysis, activation (*i.e.*, dehydration) of the alumina suppressed sulfonate hydrolysis and favored olefin formation. For example, the amount of 1-methylheptyl tosylate hydrolysis (*i.e.*, 2-octanol) decreased from 30% to 10—15% to 0—7% as the activity of the alumina was increased from I to super-I (Woelm-200) to super-I-dehydrated (Woelm-200-vacuum dried at 400 °C); octene formation increased proportionately in this series[60b]. Olefins usually are the major or even exclusive products when cyclic secondary tosylates are stirred over unactivated commercial W-200-N alumina. Based on a systematic study, it was concluded that Woelm chromatographic alumina is especially useful for concerted olefin-forming dehydrosulfonation reactions in the following instances[60b]: 1) when stereoelectronic factors strongly favor elimination in one of two possible directions (*e.g.*, 3β-cholestanyl tosylate giving only 2-cholestene); 2) when elimination of a methine β-hydrogen atom does not occur because it would lead to a bridgehead double bond; 3) when the sulfonate is symmetrical and elimination in either direction produces the same olefin; 4) when a β-elimination is possible in only one direction because there are no β′ hydrogen atoms (*e.g.*, neopentylic sulfonates).

The major disadvantages of this heterogeneous olefin-forming procedure are as follows: 1) poor regiochemical control of olefin formation when two double bond positional isomers are possible; 2) poor stereochemical control when *cis*- and *trans*-alkenes are possible; 3) indirectness (*i.e.*, alcohol→ sulfonate→ olefin); 4) large amount of alumina required for complete reaction (5—7 g Al_2O_3 per mmol of sulfonate); and 5) the inconvenience of having to dehydrate commercial alumina in order to suppress completely hydrolysis of primary and acyclic secondary tosylates.

The major advantages of this sulfonate elimination procedure are as follows: 1) inertness of many acid and base sensitive functional groups (*e.g.*, carboxylic ester); 2) concerted elimination without skeletal rearrangement of some highly rearrangement-prone tosylates (*e.g.*, neopentyl); 3) convenience of using commercially available W-200-N alumina for elimination par-

ticularly of cyclic secondary sulfonates without any significant amount of hydrolysis; and 4) ease of product isolation (*i.e.*, filtration to remove alumina and evaporation of solvent).

The practical advantages of Woelm chromatographic alumina for introducing double bonds into polyfunctional and labile compounds will make this heterogeneous "reagent" useful to organic chemists, as suggested by eq. (x)[60b].



(x)

5.4. Elimination of H—X from Alkyl Halides

Although dehydrohalogenation over alumina occurs at elevated temperatures[74], most unactivated (*e.g.*, non-allylic) halides are stable to alumina at room temperature. In contrast to homogeneous liquid phase dehydrohalogenations in which alkyl fluorides are the *least* reactive halides, alkyl fluorides are most reactive toward alumina in heterogeneous elimination reactions[75]. For example, whereas 2-iodooctane is stable toward W-200-N-dehydrated alumina for 24 h at 25 °C, 1,1-difluorocycloheptane is converted into 1-fluorocycloheptene in good yield[60b].

5.5. Elimination of H—SO_2—R

β-Elimination of a sulfinic acid on alumina has been reported to occur in a system in which an α-proton is acidified by a nitro group ($RO_2S-\underset{|}{\overset{|}{C}}-CHNO_2$)[76], and α-elimination of *p*-toluenesulfinic acid from a tosylhydrazone on alumina has been suggested as an improved procedure for generation of α-diazo carbonyl compounds[77].

6. Abstraction of Acidic Hydrogen Atoms

Unactivated C—H groups of alkanes in the gas phase can be cleaved heterolytically by alumina with abstraction of H^+ and formation of the corresponding carbanion. A linear relationship between hydrogen exchange activity and hydrocarbon acidity has been observed[78].

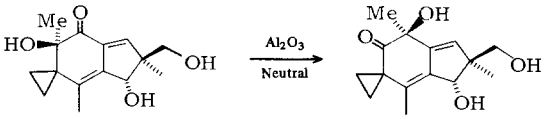
Carbonyl-activated C—H groups can be ionized by alumina to the corresponding enolate species even at room temperature. Some examples have already been given of how these alumina-generated enolate intermediates can react further in addition reactions (Section 2.2) and in substitution reactions (Section 4.2). Tritium has been introduced into keto steroids by room temperature chromatography on basic alumina previously treated with tritiated water; this heterogeneous alumina-promoted H/T exchange reaction provides pure, highly labeled ketones with remarkable economy of tracer[79]. Alumina-induced ketone enolization had also been used to epimerize C^9-H_β to C^9-H_α in an 11-keto steroid[80] and to isomerize a conjugated enone into its β,γ-unsaturated isomer in a sesquiterpene pseudoguaianolide[81].

Phosphonium-activated N—H groups can be deprotonated by basic alumina at room temperature to form ylides of the type $Ar_3\overset{\oplus}{P}-\overset{\ominus}{N}R$[82].

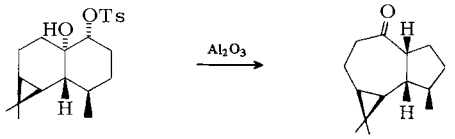
7. Skeletal Rearrangements

Alumina can act as a base, as an acid, or as a polar medium to cause molecular reorganizations in many different types of organic compounds[1].

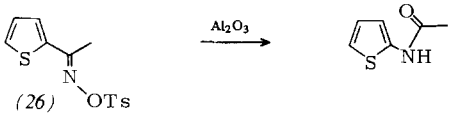
The following are a few illustrative examples. Intramolecular carbonyl addition of a neighboring methyl group in the keto alcohol *(24)* took place upon alumina chromatography[83]. Intramolecular substitution of OTs by a neighboring carbon atom in hydroxytosylate *(25)*[84] and by a neighboring thiophene group (*i.e.*, Beckmann rearrangement) of the *O*-tosyloxime *(26)*[85] occurred easily at room temperature on alumina.



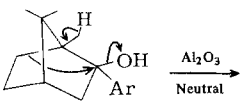
(24)



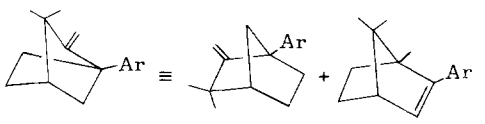
(25)



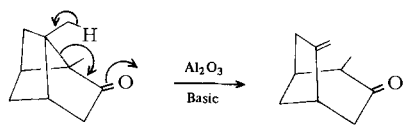
(26)



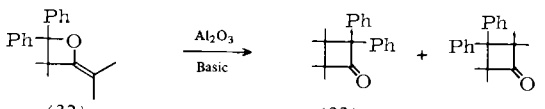
(27)



(28) *(29)*



(30) *(31)*

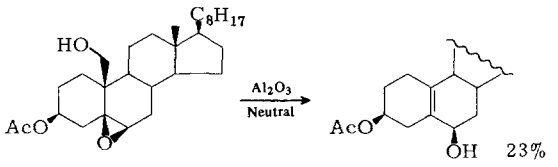


(32) *(33)* *(34)*

Overall elimination of water from tertiary benzylic alcohol *(27)* on neutral alumina produced rearranged olefin *(28)* and unrearranged olefin *(29)* in 2:3 ratio[86]. Fragmentation of carvonecamphor *(30)* *via* enolization on basic alumina gave olefinic ketone *(31)* in good yield[87], and rearrangement of isopropylideneoxetane *(32)* formed cyclobutanones *(33)* and *(34)* in 78:22 ratio[88].

8. Decarboxylation Reactions

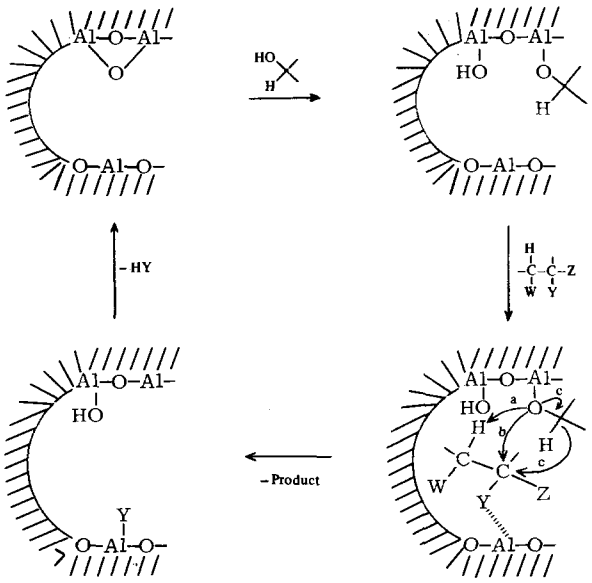
Crabbé[89] recently reported a convenient, new, and mild procedure for decarboxylation of even sensitive β-keto esters



using basic alumina in refluxing 1.5% aqueous dioxane. Loss of one carbon atom was also noted by *Morand* when the hydroxy epoxide *(35)* was exposed to alumina[90].

9. Role of the Alumina

Although much more mechanistic (*e.g.*, spectroscopic) work must be done before a detailed picture of the function of the solid support emerges, the alumina probably lowers the entropy of activation when a reactant and a reagent are adsorbed close to each other and in the proper orientation for chemical reaction[91]. Another important function of the alumina probably is to activate the reactant and/or the reagent[92]. Scheme 1 is proposed as a working model for the role of the alumina.



Scheme 1. Possible pathways of reactions on alumina.

Possibilities	Pathway	Type of reaction
Case I	a	rarely observed
W, Y = O; Z = H	b	addition
(epoxides)	c	not observed
Case II	a	enolization
W = H; Y, Z = O	b	rarely observed
(aldehydes and ketones)	c	reduction-oxidation
Case III	a	elimination
Y = OH, OR, OTs,	b	substitution
or halogen	c	not observed

Active alumina, having some strained Al—O—Al rings, is known from spectroscopic studies to cleave the heteroatom-H bonds of alcohols (*e.g.*, isopropyl alcohol is shown in Scheme 1) and of primary and secondary amines with attachment of the resultant alkoxide and amide groups to the alumina surface[93]. Because most of the reactions reported here proceed under such mild conditions, it seems reasonable to invoke also activation of the reactant by coordination of its heteroatom Y to one of the acidic aluminum atoms exposed on the alumina surface. Possible reaction pathways a, b, and c are considered for epoxides, carbonyl compounds, and good leaving groups beneath Scheme 1. Removal of HY from the alumina surface might then allow the alumina to work with high catalytic activity [see, for example, eq. (j)]. This picture of the role of alumina as a template and as an activator of reactant and reagent resembles current chemical models of the function of some enzymes.

10. Important Problems for Future Investigation

As the chemical community begins to recognize more fully the significant potential of alumina (and other solid supports) to effect some very mild and selective organic transformations, more work will probably have to be done in the following important areas: (a) understanding the physical and chemical properties of alumina surfaces and thus understanding the differences among aluminas from different commercial sources; (b) chemically and/or physically modifying the alumina surface deliberately to prepare a support having certain desired properties; (c) using alumina *catalytically*, especially in large-scale reactions; (d) forming carbon-carbon bonds *via* intermolecular reactions on alumina surfaces; (e) selectively protecting one functional group of a bifunctional molecule by selective adsorption to the alumina surface; and (f) modifying the reactivity of various known reagents by placing them on alumina.

I wish to thank publicly all of my co-workers whose names appear in the references for their many physical and intellectual contributions to our work on organic reactions at alumina surfaces. Special thanks go to Maurice Whalen, George Gurria, Al Runquist, and Donald Rogers for their very effective participation in, and stimulation of, this project. Financial support from the National Institute of Health (CA-16068) and the Research Corporation and a generous gift of alumina from ICN Pharmaceuticals and Woelm Pharma are gratefully acknowledged.

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Ion Implantation into Semiconductors

By Christian Fritzsche[*]

Ion implantation is a method of introducing foreign atoms into solids that guarantees a high accuracy even with very small amounts and very short penetrations. It is basically a way of doping solids by bombarding them with accelerated ions, and its main application lies in the manufacture of semiconductor components. The action of implantation is closely connected with the accompanying radiation damage and its repair by annealing.

1. The Role of Irradiation Techniques

The methods used for introducing foreign atoms into solids are of fundamental importance in the production of semiconductor components. These methods are used for doping, which modifies the conductivity and the type of conduction (p or n), and dopability is essential for the industrial use of a semiconductor.

In the early days of semiconductor technology, doping was accomplished by alloying with the host material in a liquid phase. However, alloying does not permit a particularly exact localization of small p- or n-conducting regions. To make transistors for high frequencies, therefore, it was necessary to turn to diffusion as a doping method. It soon became possible to produce p-n junctions at vertical distances of about 1 μm and—by the additional use of masking techniques—in lateral dimensions with a width of less than 10 μm. Taken in conjunction with the characteristics of SiO_2 layers used for the masking, the diffusion technique also offered an excellent basis for combining many components into an integrated circuit on a semiconductor chip. This gave the work a new direction in the sense that silicon became the most important semiconductor material. Further miniaturization of the components and its prerequisite, the improvement of the doping technique, promised a much greater technical advance than efforts to use other semiconductors with better physical properties.

The limits of miniaturization still have not been reached, even though an entire processing unit of a computer can now be put on a single semiconductor chip. On the other hand, the limits have already been stretched for the use of techniques in which doping is controlled by small changes in the vapor pressure and high temperatures.

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It was suggested quite early to bombard semiconductors with ions or elementary particles for accurate doping. In 1954, *Shockley*[1] applied for a patent concerning ion implantation, *i.e.* the introduction of accelerated dopant ions into the host material. This technique makes it possible to modify the properties of the host material in the vicinity of the surface. Another early suggestion, this time for uniform doping of large penetration, was to bombard the material with neutrons[2] in order to bring about the nuclear transformation of the silicon into phosphorus[3]. The introduction of irradiation techniques was delayed because of difficulties in predicting three decisive factors: the cost of the new method and the possibilities of its development, the limits of the existing methods, and the economic advantages of the attainable improvements. For the development of ion implantation a theoretical background and experience in ion beam handling was already available from nuclear physics and the physics of elementary particles. The introduction of the method into semiconductor technology was paralleled by the further development of implantation devices. We shall therefore discuss the construction of an implantation apparatus together with the requirements that arise from the technology.

2. Technique and Applications of Ion Implantation

To incorporate foreign atoms into a solid by ion implantation, these atoms must first be ionized by an ion source and the ions must then be accelerated by an electric field. The ion source and the available accelerating voltage therefore determine the possible uses and largely also the cost of the apparatus. The accelerating voltage determines—together with the charge of the ion—the ion energy and thus its depth of penetration. Presently, practical considerations impose an upper limit of 400 kV on the accelerating voltage, for semiconductor technology is already so highly rationalized that the cost-benefit ratio of an implantation apparatus is now favor-

able only if the accelerating voltage is below this value. As a result, the attainable penetration is almost invariably less than 1 μm. This is not much, but ion implantation offers great advantages over the introduction of foreign atoms by diffusion. The depth of penetration can be controlled much more accurately *via* the accelerating voltage than by the use of constant vapor pressures and constant high temperatures, particularly when small penetration depths are required. In the case of diffusion, the temperature and the vapor pressure—or instead of the latter a fixed amount of starting material—also determine the amount of substance diffusing into the solid. In the case of ion implantation, on the other hand, the amount introduced is determined by the charge, and this is the greatest advantage of the method. From the point of view of measurement, the charge-to-mass ratio is high even for heavy ions, so that the measurement of the charge is free from problems even with amounts whose accurate weighing out would be a hopeless task. For example, by using a current of 1 μA, we can transfer as little as 3.3×10^{-9} g of phosphorus in 10 s.

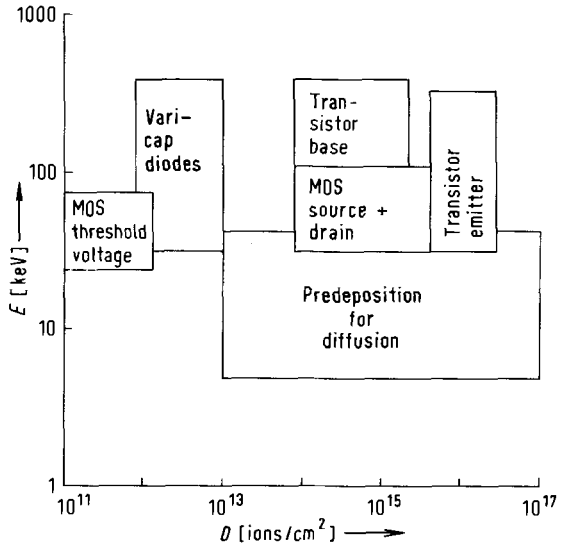


Fig. 1. Application field of ion implantation into semiconductors according to the dose D and the energy E (modified after [4]).

To show what this means for the duration of implantation and the required characteristics of the ion source, we shall first discuss the various technical applications according to the energy and the dose region, as illustrated in Figure 1. The dose is the number of ions implanted per cm^2 of the solid surface.

The smallest amount of ions is implanted for the control of the threshold voltage of MOS transistors[*]. Since this is one of the main applications of ion implantation at present, it will be briefly described here. In an MOS transistor the conductivity is controlled just below the surface with the aid of a control electrode (gate) insulated from the semiconductor. The dielectric strength and the dielectric constant of the layer insulating the control electrode permit only a limited charge accumulation, amounting to only 10^{12}—10^{13} elementary charges per cm^2 under reliable operating conditions. However, the threshold voltage at which the current flows through the transistor has to be considerably exceeded at this charge, which means that the doping must amount to 10^{11}—10^{12} atoms per cm^2. Another requirement is to control the dopant concentration to within a few percent. However, since the current flows only in an extremely thin zone below the surface, the material need be doped only to a depth of 100 nm at the most.

Therefore, to set the threshold voltage precisely, the doping must be controlled with great precision at a small depth, and it is easy to see that ion implantation is an ideal technique for this purpose.

In the other applications shown in Figure 1, ion implantation is used for making p-n junctions. Admittedly, the depths of penetration that can be achieved with energies of less than 400 keV are not always sufficiently great here, but even when one has to turn to diffusion, implantation can still be useful for first depositing an accurately controlled amount of the material that is to diffuse into the matrix. Since in the case of diffusion the implanted ions are distributed over a large vertical distance, a very high dose is needed to reach a certain concentration.

As Figure 1 shows, the various applications call for implantations in a very wide dose range of 10^{11}—10^{17} ions/cm^2. The dose D can be calculated with the aid of the formula:

$$D = It/qF$$

where I is the ion current, t is time, q is the ionic charge, and F is the surface area to be doped. Accordingly, for implanting a dose of 10^{14} ions/cm^2 over an area of 7.5×7.5 cm^2 in a few seconds an ion source supplying a current of about 200 μA is needed. This is asking a great deal, but it can be achieved with a few types of ions if a good source is used.

In such sources the ions are formed by collisions between electrons and atoms or between electrons and molecules containing the atoms to be ionized. The electrons are either drawn out from a cold cathode by the use of a high voltage (about 5 kV) (Fig. 2a), or they are emitted by a hot cathode and accelerated with about 70 V (Fig. 2b). The substance to be ionized must be either a gas, or it must be possible to vaporize it and to obtain a vapor pressure of more than 10^{-2} mbar at temperatures that can be reached in the source[5]. Therefore, ion sources to be used for making many different

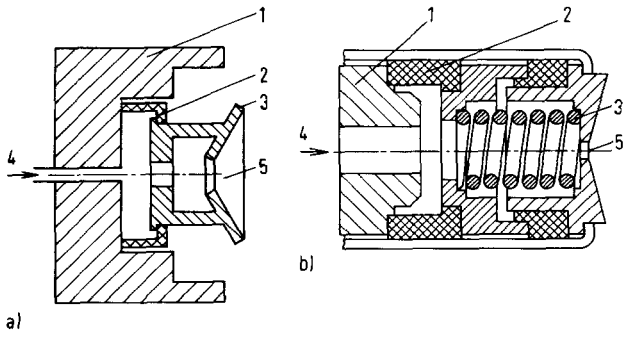


Fig. 2. Ion sources a) with a cold cathode and b) with a hot cathode: 1, anode; 2, insulator; 3, cathode; 4, gas inlet; 5, ion outlet orifice.

[*] MOS = metal oxide semiconductor. The combination of a metallically conducting layer and a semiconductor separated by an insulating layer differs from an ordinary capacitor mainly in that when the sign of the charge changes, the type of conduction near the semiconductor surface can also change.

types of ions are equipped with a small furnace from which the substance to be ionized is evaporated. Sources with hot cathodes are preferred in this case, but the cold-cathode types are more robust and more suitable for production purposes. The ion beam is drawn out (extracted) from an opening in the ion source by the use of a voltage of 20—40 kV.

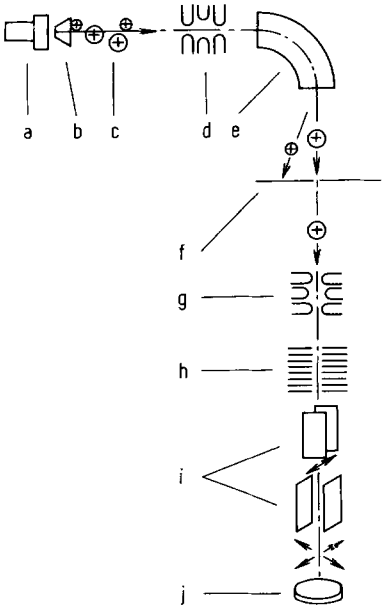


Fig. 3. Sketch of an implantation apparatus: a, ion source; b, extraction electrode; c, ion beam; d, lens; e, magnet; f, separating diaphragm; g, lens; h, accelerating electrodes; i, deflecting electrodes; j, target.

The overall construction of an implantation apparatus can now be easily understood from Figure 3. The ion source and the extraction have already been discussed. Since the source also contains some unwanted ions besides the required type, a mass separation is necessary, and this is carried out by deflection in a magnetic field. Mass separation is very valuable for scientific work, because it excludes the possibility of confusion with entrained impurities when minimal amounts are implanted. To be able to work with magnetic fields of less than 1 tesla, the ions are subjected to full acceleration only when they have passed beyond the separating magnet. For uniform implantation over large surfaces, the beam must sweep the surface. This is done either by electrical deflection of the beam or by mechanically moving the material to be doped, *i.e.* the target, with respect to the beam.

3. Penetration of Ions into Solids

Under the influence of accelerating voltages of up to 400 kV the ions reach velocities of up to 10^9 cm/s, *i.e.* 10000 km/s. What happens when ions traveling at such velocity enter the assembly of the electrons and the nuclei of atoms in the solid? It should be mentioned first of all that the ions very soon capture an electron and thus return to the neutral state, but they are still often called ions to distinguish them from the target atoms. To understand the implantation process it is important to know how the ions transfer their energy to the electrons and to the atomic nuclei of the target before finally coming to rest.

Owing to the small mass of electrons, the energy transfer to them is very different from that to the nuclei. Figure 4a shows the energy loss per unit distance of the path plotted against the energy in the case of both processes. The difference in the shapes of the curves can be explained as follows. The braking effect of the electrons on the ions resembles friction[*]. The energy loss is proportional to the velocity, and therefore decreases continuously as the energy itself decreases. The situation is different with the braking effect of the nuclei of the target atoms. This "nuclear" energy loss is calculated from the elastic collisions between charged particles. At high velocities the ion quickly traverses the electrical field of a target atom without much interaction, while at very low velocities there is little energy to transfer. In the case of intermediate velocities the transfer of energy from one nucleus to another reaches a maximum. As Figure 4a shows, the retardation by nuclei is virtually never negligible in comparison with retardation by the electrons in the energy range of interest for ion implantation. This has the following three important consequences:

1) The depths of penetration of individual ions show a large scatter, since the distance at which the ions fly past the nuclei of the target atoms is a matter of chance, and so is therefore the energy transfer. The distribution of the implanted ions is described by a mean depth of penetration (projected range) and a standard deviation. The projected range R_p for boron and phosphorus in silicon is plotted in Figure 4b *versus* the energy. The standard deviation depends on the energy and the ion-target combination and is smaller than the projected range by a factor of 1.5—4. The ranges and the energy losses have been calculated and published in tabular form for a large number of ion-target combinations[6–8].

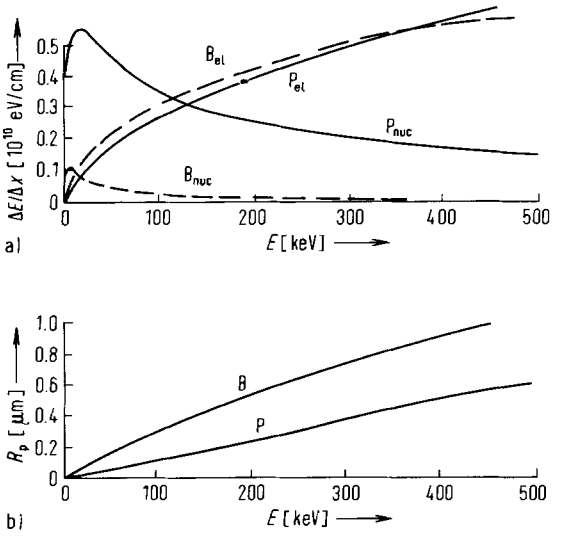


Fig. 4. a) Electronic (el) and nuclear (nuc) energy loss of boron and phosphorus ions in silicon per unit path ($\Delta E/\Delta x$) traveled; b) depth of penetration R_p of boron and phosphorus ions in silicon as a function of the ion energy E (data from [6]).

[*] It would be more accurate to compare it to electrical conduction. To determine the effect of all the electrons on the ion the relationship is reversed as it were, and the energy loss of the electrons is calculated for the case when they are scattered at an ion.

2) When nuclei collide the ions are deflected from their original direction, but this lateral spread is much smaller than the depth of penetration. For 200-keV phosphorus ions in silicon, the ratio is about 1 : 2.5, and it becomes even smaller as the energy is raised. Therefore, if the ions are implanted through a mask, the doped region has much sharper lateral boundaries than in the case of diffusion, where the lateral spread beyond the mask edge is equal to the depth of penetration.

3) Many target atoms are displaced from their sites in the crystal lattice by the nuclear collisions, causing radiation damage. Figure 4a shows that, as a phosphorus atom is being slowed down in a silicon target from 200 to 0 keV, an average energy of 0.4×10^{10} eV is transferred in nuclear collisions for each centimeter of its path. With a dose of 5×10^{14} ions/cm^2 this amounts to 2×10^{24} eV/cm^3. Since 1 cm^3 of silicon contains 5.1×10^{22} atoms, on average an energy of 40 eV is transferred per silicon atom at this dose. This is twice the energy needed to dislodge an atom that has been hit from its bonded position in the crystal lattice.

Although this simple explanation shows that ion implantation causes considerable radiation damage even at low doses, it is not suitable for quantitative estimates, because, as the dose is raised, some of the ions also collide with atoms that have already left their lattice sites, and because the atoms that have been hit only pass on some of their excess energy in nuclear collisions[9].

The transfer of energy to electrons is also involved in the occurrence of radiation damage. It causes ionization of the target atoms along the track of the ion, as a result of which, it seems, additional vacant sites arise in the crystals lattice in a region where a nuclear collision has already created a vacancy[10]. In any case, radiation damage occurring in the implantation of light ions is noticeably greater than it appears from the calculation of the nuclear energy loss. It is debatable whether the ionization of the target atoms alone leads to lattice defects in the case of semiconductors[11]. This problem is of scientific interest, because both the nature of the chemical bond and the concentration of conduction electrons must affect the course of atomic processes if the ionization facilitates the formation of defects.

4. The Effect of Nuclear Collisions

Figure 5 illustrates several possible courses of nuclear collisions. If an ion does not get close enough to a target atom, it will give up only a small proportion of its energy and change its direction only slightly. If it collides with it along a line pointing roughly to the center of the atom, it will give up much more energy to the atom than is needed to dislodge it from the lattice site. The target atom can then dislodge further atoms out of their sites in rapid succession, so that an imperfect lattice region is produced (case 1 in Fig. 5). At low energies the changes in direction are so marked that even after only a few collisions a target atom can fly out toward the surface and leave the solid (case 2). In the case of very high doses, this effect, known as sputtering, leads to a loss of the implanted ions as well. If the thickness s of the layer removed by sputtering reaches roughly the projected range R_p, the number of atoms retained in the target is already about 10 % less than the number of ions originally implanted[12]. Figure 6 shows that this can occur even at moderately high doses.

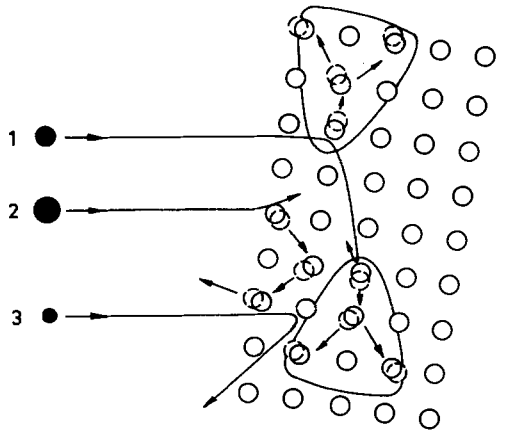


Fig. 5. Nuclear collision processes. Case 1, formation of radiation damage; case 2, sputtering; case 3, backscattering. It is customary to tilt the crystal with respect to the beam, otherwise some of the ions perform only collisions with a small angle of deflection and travel to excessively great depths along paths parallel to one of the crystal axes.

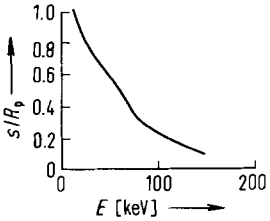


Fig. 6. Ratio between the thickness s of the layer removed by sputtering and the projected range or depth of penetration R_p, as a function of the ion energy E in the implantation of tellurium ions into GaAs at a dose of 5×10^{15} cm^{-2}.

As the dose is raised further, the concentration of the ions remaining in the target eventually reaches a limiting value, which in the case of strong sputtering is only a few atom-%. Therefore, simple chemical compounds can be prepared by implantation only when the target is not very susceptible to sputtering or the ions have a small mass.

Light ions transfer little energy to the nuclei of the target atoms and can be scattered back after an approximately central collision, so that they leave the surface altogether (case 3). Their energy then depends on the mass of the backscattering atoms and on the depth at which the back-scattering took place. The depth of backscattering in turn depends on the orientation of the crystal axis with respect to the ion beam, and on the disorder in the crystal. This is why measurement of the energy distribution of backscattered ions offers an extremely valuable method both for investigating radiation damage and for the chemical analysis of thin layers[13]. Some of the results discussed in the next section were obtained from the backscattering of H^+ and He^+ ions with initial energies of 0.3—2 MeV.

Collision with target atoms in the direction of greater depths of penetration (case 1 in Fig. 5) can lead to a special effect when the target is covered with a thin layer of another material, as in the case of a silicon target covered by an oxide layer or a layer of aluminum. If the layer thickness and the ion energy are so chosen with respect to each other that much

energy is transferred in nuclear collisions shortly before the interface has been reached, then a large number of atoms will migrate from the surface coating into the substrate. This effect is called recoil implantation. The atoms that migrate from the oxide layers are mostly oxygens, owing to their low atomic weight. Figure 7 shows by way of example the implantation of 100 keV arsenic ions into an oxide layer on a silicon substrate at a dose of $5 \times 10^{13}\,cm^{-2}$. The number of oxygen atoms introduced into the silicon per unit area by recoil implantation is plotted here against the thickness of the oxide layer. When the layer thickness is approximately the same as the projected range R_p, as many oxygen atoms are introduced into the silicon as there are arsenic atoms implanted into the oxide[14]. Oxygen is undesirable in the silicon, because it hampers the repair ("annealing") of radiation damage[15].

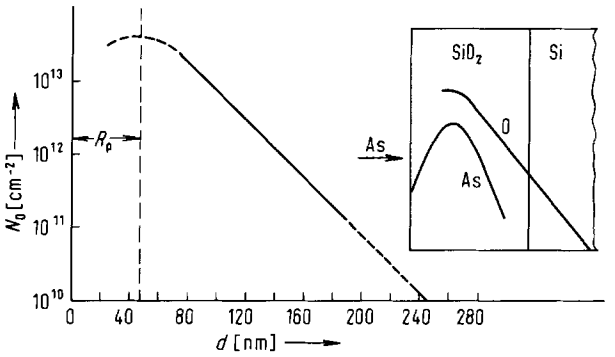


Fig. 7. Recoil implantation of oxygen from SiO_2 [14]. Primary ions: 100-keV As^+ at a dose of 5×10^{13} ions/cm^2. N_0 = number of oxygen atoms per cm^2 of silicon area, d = thickness of the oxide layer. Insert: distribution of arsenic and recoil-implanted oxygen when the oxide layer is sufficiently thick to mask against the implantation of arsenic ions.

Recoil implantation is useful if ions are to be introduced to a very small depth in a high but rapidly decreasing concentration, as for example in the case of solar cells[16]. The dopant is then applied as a thin layer onto the host and is bombarded with ions of the same or higher mass. Under favorable conditions, the number of ions introduced per unit area by recoil implantation may be fifty times as high as the dose of the primary ions.

Of the three consequences of nuclear collisions discussed above, *i.e.* radiation damage, sputtering, and recoil implantation, the first is of special importance, because it has a direct effect on the doping of semiconductors. This will be made clear in the following Section.

5. State of the Crystal Lattice after Implantation and the Doping of Semiconductors

5.1. Causes of Incomplete Doping

In most cases, ions are implanted into semiconductors for the purpose of doping. The function of the implanted ions is to act as donors or acceptors, *i.e.* to provide electrons or holes for conduction. If all the implanted ions turn into active donors or acceptors, then the number of additional charge carriers per cm^2 of surface area must be equal to the dose. However, electrical and optical measurements often indicate smaller numbers of additional electrons or holes, which may be due to the following causes:

a) The implanted ions may occupy lattice sites on which they do not become electrically active. For example, the usual doping agents for silicon must be located at substitutional sites, because on interstitial sites they remain inactive.

b) Some lattice defects may have been formed in the crystal that counteract doping either because they are electrically active themselves and are of the opposite type to the implanted ion, or because they form pairs with the implanted ions. For instance, a donor species may pair off with a vacancy in silicon to form an acceptor[17]. In compound semiconductors vacancies are available for pairing in at least two sublattices. The observed effects show a corresponding variety[18].

c) The implanted ions may diffuse to the surface and separate out there. The temperatures and times needed for annealing the radiation damage may be sufficient for a noticeable diffusion to occur.

The effect of radiation damage is not confined to the formation of electrically active defects (b), but extends to the occupation of lattice sites (a) and to diffusion (c). If we examine the way these phenomena depend on the type of the ions, the dose, and the target temperature, we find a bewildering array of effects. However, the main points already emerge from two important special cases: the formation and recrystallization of an amorphous layer, and the far reaching prevention of radiation damage by the use of high target temperatures.

5.2. Doping with Utilization of Radiation Damage

When the strongly disordered regions shown in Figure 5 (case 1) overlap with one another after the implantation of a large number of ions, an amorphous layer is formed. The disorder can then no longer be described by the number of individual defects. Figure 8a shows the disorder, determined by backscattering measurements, as a function of the dose[19]. The disorder reaches a saturation value at a dose that decreases with increasing ionic mass. In Figure 8b the disorder is expressed on the ordinate not in relative units but in the number of certain defects. Both the number and the type of the defects were determined from paramagnetic resonance[20]. The Si-G7 center (negative divacancy) was chosen as an example of defects, but other lattice defects behave similarly. The number of these centers at first increases with the dose, and at a fairly high dose centers exist whose resonance is independent of the direction. The increase in their number with a simultaneous reduction in the number of other centers indicates the change from discrete lattice defects to a fully disordered state. It is possible to show by electron diffraction or with a scanning electron microscope that an amorphous region is formed when the radiation damage reaches saturation[21–23]. The amorphous layer recrystallizes in contact with the crystalline substrate even at moderate temperatures (550—650 °C for silicon). Impurity atoms that can replace the atoms of the semiconductor in the crystal lattice mostly occupy a large proportion of these substitutional sites during recrystallization. This is why the formation of an amorphous zone can be very useful, as shown in Figure 9[24]. These curves indicate the number of conduction electrons under 1 cm^2 of the surface after the implantation of antimony into silicon and subsequent annealing at various

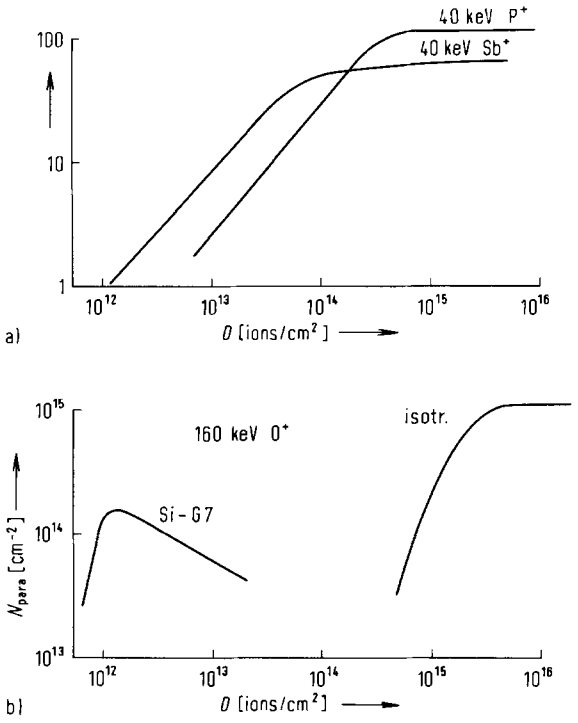


Fig. 8. Dose-dependence of radiation damage in silicon. a) Disorder determined by backscattering (relative units) [19]; b) number of paramagnetic defects N_{para} [20]. D = dose.

temperatures. If all the implanted ions turn into active donors, this number must be equal to the dose. With a dose of 1.5×10^{13} antimony atoms per cm^2 (curve b) no amorphous layer is yet formed. The proportion of active donors increases slowly with the annealing temperature and does not yet reach the maximum when this temperature is raised to 800 °C. With

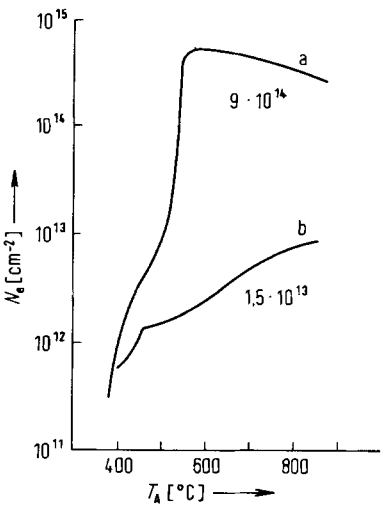


Fig. 9. Electrical activity of 40-keV antimony ions implanted into silicon [24]. N_e = number of electrons per cm^2; T_A = annealing temperature.

a dose of 9×10^{14} ions per cm^2 (curve a) the number of ions is well above the critical dose needed for the formation of an amorphous layer. As soon as the amorphous layer recrystallizes, the proportion of ions that function as active donors sharply increases to a maximum.

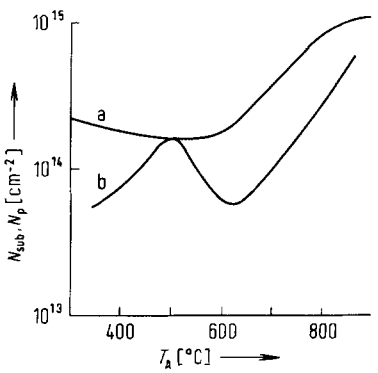


Fig. 10. Electrical activity of boron ions implanted into silicon. a) N_{sub} = number of boron atoms per cm^2 on substitution sites; implantation energy 56 keV, dose 1.2×10^{15} ions/cm^2 [29]; b) N_p = number of free charge carriers (holes) per cm^2; implantation energy 40 keV, dose 1.0×10^{15} ions/cm^2 [27]; T_A = annealing temperature.

In the case of phosphorus this sudden increase in the proportion of active species occurs even at a low dose[25, 26] as soon as the defects are repaired. Boron implantations commonly do not exceed the critical dose, and the proportion of active boron ions at a low dose does not increase either suddenly or monotonically but instead passes through a maximum and then a minimum. Comparison between electrical measurements[27] and backscatter measurement[28, 29] indicates that the processes mentioned under Point b) in Section 5.1 play an important role here. In fact, the electrical activity and the number of boron ions on substitutional sites vary differently with the annealing temperature (Fig. 10). To reach a high activity also with boron after a moderate annealing temperature, one can implant the ion of a heavy boron compound such as BF_2^+[30], formed from boron trifluoride in the ion source. Here a dose of 1×10^{15} ions/cm^2 already leads to the formation of an amorphous layer, in the recrystallization of which over 90 % of the boron atoms become electrically active[*].

5.3. Doping with Utilization of Self-annealing

The maximum electrical activity of the implanted ions cannot always be reached by the annealing of the amorphous layer. It may be better to suppress to a great extent the occurrence of radiation damage in the first place, by heating the target during implantation. The temperature needed for this is lower than the recrystallization temperature after implantation, because the collisions of ions rupture chemical bonds. When the bonds have re-formed, which takes about 10^{-9} s, the inside of the disordered region will be amorphous and its edges will be crystalline. Crystallization requires diffusion processes, and the higher the temperature of the target the faster these proceed within the 10^{-9} s period[32]. It should be mentioned that we are speaking here of a disordered zone along the path of a single ion and not of the whole amorphous layer, which arises from the aggregation of the individual zones only at a high dose.

[*] The high activity is not the only advantage of BF_2^+ implantation. The amorphous layer also prevents the migration of defects on annealing in oxidizing atmospheres and so enables the manufacture of implanted p-n junctions with low leakage currents [31].

Figure 11 illustrates the effect of this self-annealing during implantation in the case of GaAs, by showing how the disorder (determined by measuring the back-scatter of He ions) varies with the target temperature[33]. It can be seen that even temperatures of 100—200 °C greatly reduce radiation damage, and hardly any disorder is noticeable at 350 °C. Figure 12 shows the favorable effect of an elevated target temperature on the activity of selenium ions in GaAs[34]. The curves have been

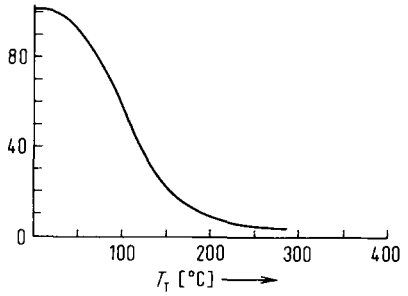


Fig. 11. Lattice disorder in GaAs (arbitrary units) [33] after the implantation of 40-keV tellurium ions at a dose of 5×10^{15} ions/cm^2; T_T = target temperature.

obtained by plotting the charge-carrier concentration against the depth in the target. The maximum is expected at 70 nm, and it does come there at 350 °C, with the concentration

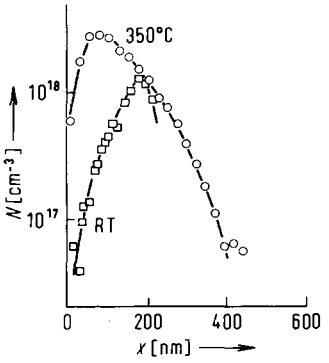


Fig. 12. Implantation profile of 400-keV selenium ions in GaAs for two target temperatures T_T [34] at a dose of 1×10^{14} ions/cm^2, after annealing at 900 °C. The depths of penetration do not agree with the theoretical value because the ions were implanted through a protective layer of Si_3N_4. RT = room temperature, N = density of free charge carriers, x = depth below the surface.

corresponding to an electrical activity of 80 %. When the implantation is carried out at room temperature, the activity decreases particularly in the region in which radiation damage is the most extensive. When doping PbTe it is also advisable to allow the radiation damage to "repair" already during the implantation. However, the self-annealing is so strong here that the target must be cooled with liquid nitrogen if an amorphous layer is to be obtained[35].

5.4. Residual Damage, Diffusion Losses, and Choice of Conditions of Implantation and Annealing

It seems to be a property of compound semiconductors in particular that in many cases heating to the highest technically practicable temperature is still not sufficient to abolish the effect of radiation damage on the electrical activity. Perhaps this can be explained by the high stability of defect pairs formed from a doping atom and a vacant site in the appropriate sublattice of the compound. The vacancies can be filled by implanting not only the dopant but also the component of the compound that corresponds to the vacancies, or by covering the semiconductor, prior to annealing, with a protective layer that contains this component.

A residual radiation damage remains also in elemental semiconductors after high-temperature annealing, but—unlike in many compound semiconductors—it is manifested not so much in a reduction of the electrical activity as in a reduced mobility[27, 36] and lifetime[37] of the charge carriers. This is because of the transformation of the original or primary defects into secondary defects, especially dislocations, which under unfavorable conditions do not disappear in silicon even at 1100 °C[38]. The type and the magnitude of the secondary defects depend on the conditions of implantation, the type of the ions used, the annealing temperature, and the atmosphere in which the annealing is carried out[39, 40]. However, they have significant disadvantages only when the dose exceeds 5×10^{14} ions/cm^2[41].

The reduction of the electrically active proportion of the implanted ions by outward diffusion may be mentioned here briefly. Ions that easily diffuse at the required annealing temperatures (*e.g.* Sb in Ge) must be implanted to a greater depth if one wants to prevent a significant part from diffusing

Table 1. Electrical activities of ions implanted into Si and GaAs as a function of the conditions of implantation and annealing (RT = room temperature).

Target	Ion	Electr. activity [%]	Dose [ions/cm^2]	Energy [keV]	Impl. temp. [°C]	Annealing temp. [°C]	Protective layer	Ref.
Si	B	100	10^{15}	40	RT	950	—	[27]
Si	B	100	10^{15}	40	−196	550	—	[27]
Si	Al	70	10^{13}	30	RT	650	—	[42]
Si	Al	30	10^{14}	30	RT	900	—	[42]
Si	P	90	5×10^{15}	280	RT	600	—	[26]
Si	As	100	3×10^{15}	280	RT	600	—	[26]
Si	Sb	50	5×10^{14}	30	RT	600	—	[42]
Si	Bi	10	2×10^{14}	40	RT	600	—	[42]
GaAs	Be	100	10^{14}	250	RT	900	Si_3N_4	[45]
GaAs	Zn	100	10^{15}	150	RT	850	SiO_2	[43]
GaAs	Cd	100	10^{14}	135	RT	850	Si_3N_4	[44]
GaAs	Si	70	10^{13}	400	RT	850	Si_3N_4	[32]
GaAs	S	100	2×10^{12}	350	RT	850	SiO_2	[46]
GaAs	S	16	10^{14}	1000	RT	825	Ga—SiO_2	[47]
GaAs	S	40	10^{14}	1000	360	825	Ga—SiO_2	[47]
GaAs	Se	66	10^{14}	400	350	900	AlN	[48]
GaAs	Te	26	10^{14}	400	350	900	AlN	[48]

out[41]. The diffusion may be promoted by the continuous formation of defects during the implantation (radiation-enhanced diffusion).

Recently, the annealing of radiation damage by laser irradiation has attracted considerable attention. The sudden and intense supply of energy by the laser obviously affects the lattice defects in an essentially different way from continuous heating in a furnace. Tellurium in GaAs could be incorporated almost completely at substitutional sites even for concentrations which exceed the known solubility more than tenfold[67]. However, the conductivity did not exceed that obtained by conventional doping. High electrical activity was also achieved for boron in silicon by laser annealing[68]. Irradiation at a sufficiently high energy per laser pulse apparently produces a liquid phase such that epitaxial crystal growth from the liquid can replace the recrystallization in the solid state[69]. Particularly for Si, the depth distribution of the ions after laser annealing does not correspond to the Gaussian distribution obtained by the implantation[68, 70]. The technical interest in laser annealing results both from the high electrical activity achievable in a relatively short time and from the possibility of confining the heating of the material to the implanted zone.

To sum up, the factors causing a reduction of the electrical activity and mentioned at the beginning of this section can be combated mainly by a suitable choice of the temperature during implantation and the annealing of radiation damage, but the results depend to a great extent on the dose, the depth of penetration, additional implantations, and the use of protective layers during annealing. The data in Table 1 show the electrical activity of implanted ions in Si and GaAs after implantation and annealing under various conditions.

6. Implantation into Silica Layers and Interfaces

One of the most important structures in semiconductor technology is the combination of a silicon wafer with a thin layer of silica. This layer can serve as a mask for diffusion and implantation processes, it stabilizes the silicon surface, and it is used in MOS transistors as an electrically insulating layer. We shall deal here only with the layers obtained by the thermal oxidation of silicon. The main effects in ion implantation are as follows:

In the case of implantation before oxidation: influencing the rate of oxidation through the implanted ions; and influencing the radiation damage through oxidation.

In the case of implantation after oxidation: radiation damage in the oxide; and recoil implantation of oxygen (see Section 4).

The effect of radiation damage on the rate of oxidation is only temporary, since the oxidation temperatures are well above the annealing temperature. Some doping elements have a direct effect on the oxidation rate. Antimony can accelerate the growth of the oxide layer by a factor of 6, but it must be implanted in a concentration of about 10^{21} ions/cm^3 for this to happen. When the oxidation extends beyond the implanted layer, the effect rapidly decreases[49, 50]. Implanted nitrogen can reduce the growth of the oxide layer by a factor of more than 10. It is assumed that nitrogen is pushed to the surface during the recrystallization of the silicon. The concentration thus rises until it is sufficient for the formation of an Si_3N_4 layer, which protects the silicon from oxidation[51].

As mentioned in Section 5, dislocations are formed when the radiation damage is annealed in silicon. In the case of thermal oxidation the dislocation loops can become so large that they can be seen under an optical microscope after chemical etching[52]. We must anneal the radiation damage before oxidation or ensure a slow oxidation if we want to avoid the undesirable effect of the radiation damage on the electrical characteristics of the components[53].

Oxide layers are often used to shield parts of a silicon surface from implantation, or the ions are implanted through an existing oxide layer. The radiation damage that then arises in the silica can be studied very easily by examining the optical properties of silica. Figure 13 shows by way of example

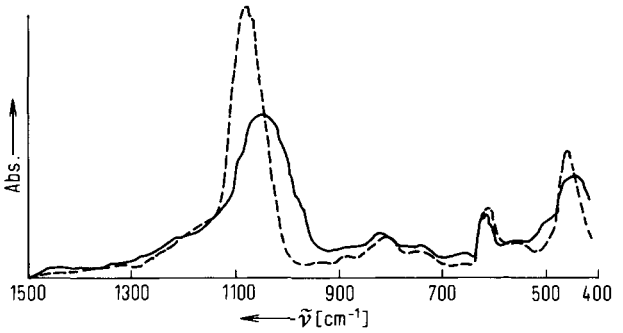


Fig. 13. Absorption spectra of SiO_2 layers [54] with implanted phosphorus (full line) and without it (broken line). The band at 620 cm^{-1} is due to the much thicker silicon substrate.

the IR spectra of two silica layers on silicon, one with and the other without implanted phosphorus ions. The result of the bond rupture due to implantation is that the band near 1100 cm^{-1} is shifted and the area under it is reduced. However, the original spectrum is re-established when the material is heated to 690 °C for 50 min[54]. Although thermally grown oxide layers are amorphous, they show saturation of radiation damage at a certain dose, similarly to crystalline materials. This indicates that amorphous layers are not structureless and that ion implantation results in a special type of disorder.

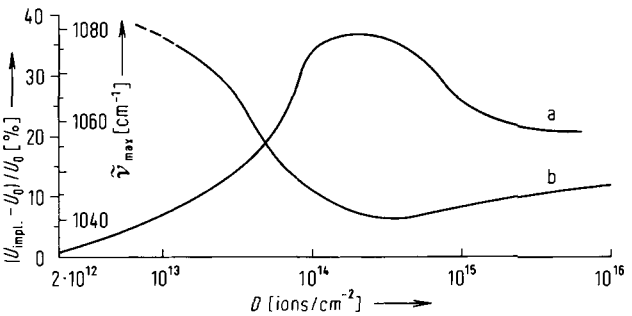


Fig. 14. Dose dependence of the change in the dielectric breakdown (a) and the position of IR absorption in silica implanted with phosphorus (b) [56]. U_0 = breakdown voltage without implantation. U_{impl} = breakdown voltage after implantation, $\tilde{\nu}_{max}$ = wave number of the principal band, D = dose.

The electrical properties of the boundary surfaces between silica and silicon, which are very important for MOS transistors, are not, it seems, directly connected with disorder in the oxide. Although the density of the surface states is raised

by the implantation of ions, it rapidly decreases again even at an annealing temperature of only 200 °C[55], *i.e.* well before the radiation damage in the silica has been repaired. In contrast, the implantation-induced increase in the dielectric strength[56] is clearly connected with the shift of the absorption band and thus with the disorder (cf. Fig. 14). The disorder makes the free path of the electrons shorter and thus reduces the probability that an electron will be accelerated until it reaches the energy needed for ionization on collision.

The effect of ion implantation on dielectric breakdown is of scientific rather than of practical interest, but it does show that ion implantation is not only a technological process but also a useful tool for scientific investigations, important examples of which have been collected by *Schulz*[57].

7. Miscellaneous Applications, Limitations, and Future Development of Ion Implantation

Besides the doping of semiconductors, ion implantation has many other possible applications of varying technical importance. The preparation of SiC, Si_3N_4, and SiO_2 by implantation into silicon is possible but has no prospects[58, 59, 54]. Other topics of research are the modification of the magnetic properties of garnet layers[60], the preparation of superconductors[61, 62], and the modification of friction and wear[63].

If we extend the diagram shown in Figure 1 to even higher doses and extremely low energies of between a few hundred electron volts and 40 eV, we come to the field of ion beam deposition of thin layers[64, 65], but this will not be discussed here because it is very different from ion implantation both as regards the apparatus used and the physical problems involved.

It should be pointed out that the fascinating advantage of ion implantation—its excellent reproducibility—does not mean an absolute accuracy of the dose and the depth of penetration. The accuracy is limited both by problems connected with the apparatus, the solution of which is very costly, and by insufficient knowledge of some side effects[66]. The beam deflection system alone introduces inaccuracies, because, at the same change in the angle, the area bombarded differs with the angle, particularly when the target is not normal to the beam. Yet with single crystals the target must be tilted with respect to the beam by about 7° to minimize deviations from the normal spatial distribution of the implanted ions. Such deviations are caused by ions whose paths largely run along definite preferred crystallographic directions, which makes a longer range possible. We have already mentioned the loss of ions through sputtering. It is often forgotten that light ions can be reflected at a target of high atomic weight. In the implantation of aluminum into cadmium mercury telluride, for example, this can introduce an error of up to 20 % into the dose. In unfavorable cases the fluctuations in the vacuum inside the beam guidance system and variations in the composition of the residual gas in the ion source can limit not only the accuracy but also the reproducibility. Charge variations and the decomposition of molecule-ions have an adverse effect on the uniformity of the depth of penetration and the beam deflection. Ions of the same mass such as CO^+, N_2^+, and $^{28}Si^+$ cannot be separated, and their proportions in the beam can be estimated only roughly from the intensity of the accompanying ions, in this case C^+, O^+, and N^+.

However, except for the error involved in the beam deflection angle, these sources of error are noticeable only in special cases. Ion implantation has proved to be an outstanding doping technique. Besides, the more widely it is used, the more attractive is its application for regulating the course of certain technical processes such as oxidation and etching. The need to make semiconductor components smaller and smaller and to combine more and more of them in integrated circuits calls for costlier apparatus not only for doping but also for masking and etching techniques. This trend must be taken into account when considering the future development of the implantation technique, and it can be assumed that ion implantation will not remain merely a complement of the diffusion technique but will instead lead to fundamental changes in technical concepts when all the innovations have been combined.

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Cobalt-Catalyzed Pyridine Syntheses from Alkynes and Nitriles

New synthetic methods (23)

By Helmut Bönnemann[*]

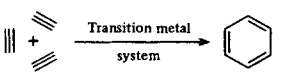
Soluble organocobalt catalysts permit selective formation of substituted pyridines under mild conditions in a single step: mono-, di-, and trisubstituted pyridines can be obtained at will in high conversions and high yields from nitriles and alkynes. Polynuclear derivatives such as bipyridines can also be prepared by this method.

1. Introduction

During the past 15 years, the use of homogeneous transition metal catalysts in olefin chemistry has made numerous useful hydrocarbons available from simple starting materials. The relation between the structure of the catalyst and its mode of action has, in many cases, been largely elucidated (cf. refs. [1, 2]). In contrast, relatively few investigations have been made on the metal-catalyzed syntheses of heterocycles[3]. This is understandable since many metal catalysts are blocked when hetero atoms such as nitrogen, oxygen, or sulfur are present in the substrate.

Starting from the discovery that the perturbing influence of polar groups on cobalt as the central atom of a homogeneous catalyst is apparently very slight[4], heterofunctional substrates were allowed to react in the presence of organocobalt catalysts.

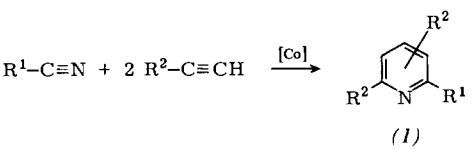
Cyclotrimerization of alkynes to give benzene derivatives [eq. (a)] was adopted as a "model reaction" for systematic studies on the use of soluble cobalt catalysts in the synthesis of heterocycles.



(a)

Many variants of this long-known reaction have been studied. It is a typical metal-catalyzed organic reaction, proceeding with a wide range of transition metal systems such as carbonyls, metallocenes, and even simple salts (cf. refs. [5-8]). Cobalt was found to be one of the most effective catalyst metals for the reaction shown in eq. (a).

The very first attempts to use cobalt for the synthesis of heterocycles revealed that a C≡C bond could be replaced by a C≡N bond in the standard cyclization procedure [eq. (a)]: reaction of both alkynes and nitriles on cobalt catalysts



(b)

(1)

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in homogeneous phase afforded a pyridine derivative of type *(1)* as the main catalytic product.

Delineation of the scope of this approach soon showed that eq. (b) provides a new general catalytic pathway to pyridine derivatives[9, 10].

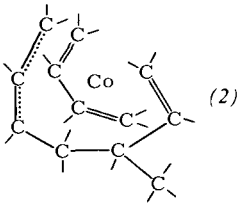
Before considering the preparative implications, let us first examine the nature of the catalysts.

2. Survey of the Organocobalt Systems Employed

2.1. Organocobalt Complexes

A series of "ready-made" organocobalt complexes can be used for the synthesis of pyridines.

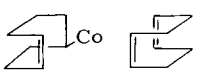
Reaction usually proceeds smoothly on *allylcobalt* systems. The preparation and properties of these species have been reported elsewhere[11]. A typical representative of this class of catalysts is butadiene(5-methylheptadienyl)cobalt *(2)*[12]. All the organic constituents of compound *(2)* are derived from butadiene.



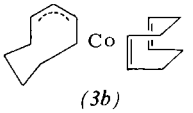
(2)

The red crystalline complex *(2)* is formed on reduction of a solution of cobalt(II) chloride and butadiene in ethanol at −30°C with $NaBH_4$. Two butadiene units combine to form a methyl-substituted C_7 chain which is bonded to the cobalt atom *via* the π-allylic system and the terminal vinylic group. Pure *(2)* is thermolabile and must be stored and handled below −30°C.

More suitable for practical applications in catalysis are the 1,5-cyclooctadiene(cyclooctenyl)cobalt complexes *(3a)* and *(3b)*. These compounds may be stored at 20°C and may be prepared by reduction of cobalt salts with triethylaluminum[13], metals[14] or electrochemically[15] in the presence of 1,5-cyclooctadiene (COD).



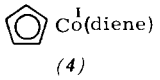
(3a)



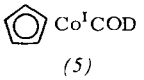
(3b)

The σ form *(3a)* and the π isomer *(3b)* show the same selectivity in pyridine synthesis.

An important role in the catalytic reactions shown in eq. (b) is played by *cyclopentadienylcobalt(I) systems:* the π-cyclopentadienyl group confers considerable thermal stability upon the complex.



(4)

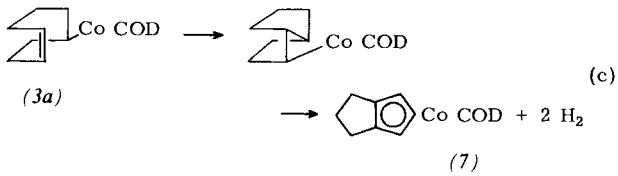


(5)



(6)

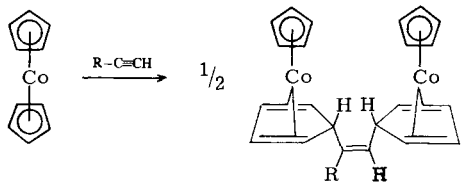
This class of compounds *(4)* containing a CpCo core complex *(6)* is considered to include *(7)*, which is obtained according to eq. (c) by intramolecular ring closure and elimination of hydrogen from *(3a)*. *(7)* can also be prepared from the π form *(3b)*[15].



(3a) (c) *(7)*

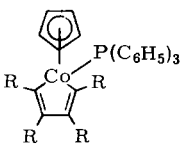
Diamagnetic cobalt(I) complexes with a central unit *(6)* stabilized by ene and diene systems are known in various guises[16–20] and are readily accessible. Our previous experience has shown that all systems containing a central unit of type *(6)* are effective catalysts for the pyridine synthesis, regardless of the kind of stabilizing olefinic ligand present.

This series of "ready-made" cobalt catalysts for the pyridine synthesis could be extended at will: the only basic requirement is that the complex ligands should be completely or partly displaceable from the metal by the nitrile or alkyne—the active cobalt(I) species is liberated and catalysis occurs. Cobaltocene can also be used in this way[21, 22]; an initial activating step, eq. (d), gives a system containing the essential core structure *(6)*[21].



(d)

Similar observations have been reported for the phosphane-modified cobalt(III) complexes *(8)*. *Yamazaki* and *Wakatsuki* obtained pyridine derivatives with the aid of such systems as early as 1973[23] while our work on phosphane-free systems was in progress.

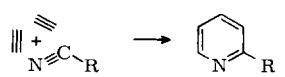


(8)

The species *(8)* contains two acetylene molecules linked together at one end and joined *via* a cobalt atom at the other to form a five-membered ring. However, the Japanese authors report the synthesis of *(8)* to be troublesome, and subsequently they also adopted simple organocobalt complexes such as cobaltocene for use as catalysts[21, 23c].

2.2. Catalysts Generated *in Situ*

Synthesis of pyridines from alkynes and nitriles [eq. (e)] can be carried out advantageously in a one-pot reaction; the cobalt catalysts then being generated *in situ*[9, 10].



(13) + *(12)* *(14)* (e)

Prior to the initiation of catalysis, a small amount of a suitable cobalt salt is dissolved or suspended in the substrate

mixture and a solvent is added if required. The next step consists in activation with reducing agents, the anions being removed from the cobalt and the vacant coordination sites being occupied by substrate molecules. Metals of the 1st to 3rd Main Groups, and their hydrido or alkyl compounds, are especially suitable as reducing agents. If complex formation with the substrates is insufficient to stabilize the cobalt atom in solution, additional "stabilizers" can be introduced before the reduction step. Cyclic olefins (*e.g.* the chelating diolefin 1,5-cyclooctadiene) are particularly suitable as stabilizing agents. In contrast to the situation with Ziegler catalysts, the organometallic species serves merely as reducing agent. It is not an integral component of the catalyst and thus of no importance for the actual catalytic reaction. Examples are shown in Table 1.

Table 1. Catalysts for pyridine synthesis generated *in situ* [eq. (e)].

No.	CoX_n/Metal	No.	CoX_n/MH	No.	CoX_n/MR
(9a)	$CoCl_2$/Li [a]	*(10a)*	$CoCl_2$/LiH	*(11a)*	$CoCl_2/C_4H_9Li$
(9b)	$CoCl_2$/Na [b]	*(10b)*	$CoCl_2/LiAlH_4$	*(11b)*	$CoCl_2/C_2H_5MgX$
(9c)	$CoCl_2$/Mg [c]	*(10c)*	$CoCl_2/NaBH_4$	*(11c)*	$Co(acac)_3/(C_2H_5)_3Al$
(9d)	$Co(acac)_3$/Mg [c]	*(10d)*	$Co(OAc)_2$/ $Co(acac)_2$/ $Co(HCO_2)_2$ } $NaBH_4$	*(11d)*	$Co(acac)_2/(C_2H_5)_2AlOC_2H_5$

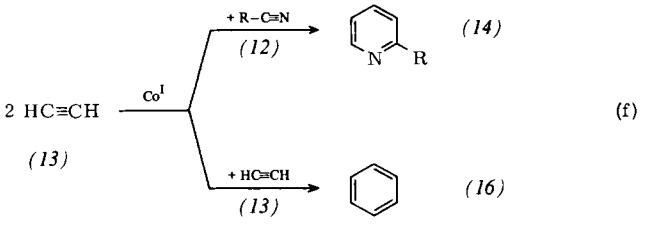
[a] Reduction in the presence of the nitrile *(12)*; the acetylene *(13)* is added subsequently. [b] Subsequent addition of the nitrile *(12)*. [c] Activated with iodine.

The cobalt salts, *e.g.* $CoCl_2$, can be used in hydrated form. Use of an inert atmosphere and additional stabilizing ligands such as phosphanes, is unnecessary. The system *(15)* has proved most valuable in the laboratory:

$$CoCl_2 \cdot 6\ H_2O/2\ NaBH_4 + \text{Nitrile/Alkyne} \qquad (15)$$

3. Catalytic Synthesis of 2-Substituted Pyridines

2-Substituted pyridines of type *(14)* are readily obtained in solution from carbonitriles *(12)* and acetylene *(13)* [eq. (e)] in the presence of "ready-made" organocobalt catalysts (Section 2.1). Whereas the nitriles *(12)* undergo practically exclusive conversion into the pyridine derivatives *(14)*, if no special precautions are taken[*] the alkyne component always undergoes some degree of conversion into benzene derivatives *(16)*. The ratio of heterocyclic to carbocyclic products (*i.e.* *(14)*:*(16)*) determines the preparative value of the synthesis and can be directed in favor of *(14)* by using an excess of the nitrile *(12)*.



(f)

[*] *Vollhardt*'s generalization that co-cyclization of monoacetylenes with nitriles leads to "complicated mixtures" [132] is not justified and is presumably based on a misinterpretation of the data published by us [10, 24] and *Wakatsuki* [21, 23].

If catalysis [eq. (f)] is conducted in the presence of a permanent excess of nitrile and the stoichiometric amount of alkyne is added at such a rate that the steady-state concentration of the C≡C bond remains as low as possible, the heterocycles *(14)* can be obtained in yields exceeding 90 % without significant formation of by-products *(16)*. About 1 mol-% of catalyst is first dissolved in pure nitrile to give a brown solution without deposition of metal; these solutions are drawn into a V4A autoclave. Acetylene is then added at 20 bar up to a pressure of 11 bar[*]. The autoclave is heated to 120—130 °C for 1 h, whereupon the pressure drops to *ca.* 9 bar. The pressure is then raised to *ca.* 16 bar and the acetylene consumed is continuously replaced. After *ca.* 2 h, the stoichiometric amount of acetylene has been consumed and the catalytic reaction [eq. (e)] is complete. This modified procedure readily affords 2-substituted pyridines *(14)* (Table 2). The catalyst systems *(3)*, *(5)*, or *(11)* produce 100 to 400 mol of *(14)* per mol of catalyst.

Table 2. 2-Substituted pyridines *(14)* obtained according to eq. (e). [Catalyst *(11)* or *(5)*; reaction temperature 120—130 °C; almost complete conversion; work-up by distillation.]

R	Yield [%]	B.p. [°C/torr]	n_D^{20}	M^+ (*m/e*) [a]	Product known according to ref.
CH_3	93	129/760	1.5005	93	[25–42]
C_2H_5	96	150/760	1.4968	107	[25, 31, 32, 36, 43–46]
C_4H_9	89	188/760	1.4892	135	[32, 36, 47–49]
C_5H_{11}	97	104/17	1.4834	149	[32, 50]
C_6H_{13}	96	111/15	1.4837	163	[32]
C_7H_{15}	98	122/13	1.4852	177	[32]
C_8H_{17}	96	109/8	1.4830	191	
C_9H_{19}	95	105/1.5	1.4866	205	[51–53]
$C_{10}H_{21}$	91	125/0.01	1.4810	219	
$C_{11}H_{23}$	96	166/7	1.4807	233	
$CH{=}CH_2$	78	50–60/13		105	[39, 43, 44, 54–64]
C_6H_5	89	146/16	1.6182	155	[39, 57, 65–68]
$C_6H_5CH_2$	94	147/15	1.5781	169	[29, 31, 69–72]

[a] Further IR and ^{1}H-NMR spectra are available for the major fraction.

As discussed for eq. (f), the product selectivity of the cobalt catalyst with respect to *(14)* or *(16)* can be influenced by a suitable choice of the nitrile/alkyne ratio. This result suggests that the product selectivity in eq. (f) might be controlled by further ligands complexed to the cobalt. Moreover, the catalytic reaction could possibly show a control effect in strongly polar solvents such as tetrahydrofuran, alcohols, or amines which can coordinate to transition metals. Several series of comparative studies show, however, that

[*] Special safety precautions must be observed on working with acetylene under high pressure (> 3 bar).

1) The product selectivity is independent of the catalyst type; compounds *(2)* to *(4)* and *(8)* to *(11)* were examined;
2) Phosphanes, arsanes, and Lewis acids have no effect[*];
3) Strongly coordinating solvents such as cyclic ethers, chlorohydrocarbons, amines, or alcohols lower the rate of eq. (f) but do not affect the product ratio *(14)*:*(16)*.

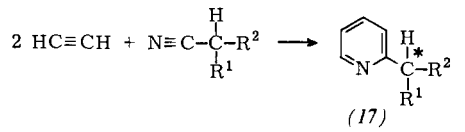
These observations justify the conclusion that the selectivity of the cobalt catalyst of eq. (f) is subject only to "substrate control".

In order to compare the turnover numbers (measured as number of mols of pyridine per mol of cobalt and hour) of soluble organocobalt catalysts we performed the standard reaction of eq. (e) at 130°C and 13 bar of acetylene under the same conditions but with various catalysts. The results of this comparative study are listed in Table 3.

Table 3. Efficacy of various catalyst types in reaction according to eq. (e) [130°C/13 bar acetylene, R = phenyl]. As soon as a drastic drop in acetylene uptake was observed catalysis was discontinued and the products worked up.

	Catalyst type	Conversion of RCN [%]	$\frac{\text{mol } (14)}{\text{mol CO}\cdot\text{h}}$
(10d)	$Co(OAc)_2/Co(acac)_2/Co(HCO_2)_2/NaBH_4$	93	595
(11c)	$Co(acac)_3/Et_3Al$	96	621
(11d)	$Co(acac)_2/Et_2AlOEt$	94	640
(15)	$CoCl_2\cdot 6H_2O/2\,NaBH_4$	94	590
(9a)	$CoCl_2$/Li	95	595
(5)	CpCo(COD)	97	618
(3b)	$C_8H_{13}Co(COD)$	94	580
(2)	$C_8H_{13}CoC_4H_6$	92	400
(8)	$Cp(R_4C_4Co)PPh_3$, R = phenyl	90	120
	Cp_2CO	92	12
	$CpCo(CO)_2$ [73]	40	2

Table 3 also clearly reveals the inhibitory action of carbonyl and phosphane groups on the catalysis [eq. (e)]. The best catalysts are systems reduced *in situ* as well as compounds containing the cyclopentadienylcobalt group.



(17)

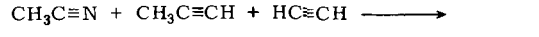
(g)

The only method so far available for selective synthesis of 2-substituted pyridines, *i.e.* cobalt-catalyzed reaction of nitriles with acetylene [eq. (e)], has also acquired industrial importance. In this context, particular interest is attached to 2-picoline (2-methylpyridine) that is used mainly for the production of 2-vinylpyridine.

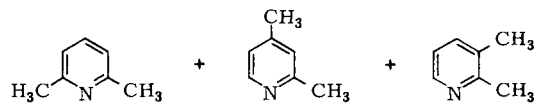
2-Vinylpyridine, which is also directly accessible from acetylene and acrylonitrile according to Table 2, is used as a terpolymeric grip promoter in the tire industry. Moreover, it is also employed as comonomer in the polymerization of acrylonitrile in order to improve the dyeing properties of acrylic fibers.

4. Catalytic Synthesis of Lutidines

Reaction according to eq. (e) can also be conducted as a co-cyclotrimerization by using two different alkynes [eq. (h)]. For instance, simultaneous reaction of acetylene, propyne, and acetonitrile in presence of catalyst *(5)* affords a mixture of dimethylpyridines (lutidines) *(18)* together with 2-methylpyridine and isomeric trimethylpyridines.



(h)



(18a) *(18b)* *(18c)*

Table 4. Lutidines *(18)* and ethylmethylpyridines obtained according to eq. (h) [catalyst *(5)*].

Products	Isomeric distribution [%] [a]	Yield [%] [b]	B.p. [°C/torr]	n_D	M^+ (*m/e*)	Products known according to ref.
(18a)	65	33	143/770	1.4953^{25}	107	[31–33, 76–78]
(18b)	28		159/760	1.4984^{25}		[31–33, 45, 46, 76, 79–82]
(18c)	7		160/760	1.5057^{20}		[32, 33, 45, 46, 80–83]
2-Ethyl-6-methylpyridine	65	31	160/760	1.4941^{16}	121	[45, 46, 80, 82, 84]
2-Ethyl-4-methylpyridine	35		173/748			[45, 82, 85, 86]

[a] According to gas chromatography. [b] Identified by ^{1}H-NMR spectroscopy, separated by gas chromatography.

Prompted by a preliminary report[74] of our new catalytic synthesis of 2-substituted pyridines, *Botteghi* applied the technique to the catalytic synthesis of analogous optically active derivatives[75]. Thus optically pure *sec*-butyl cyanide, which is readily accessible by classical methods, on cyclization with acetylene above 7 bar at 140°C with catalyst *(5)* affords the corresponding optically active 2-*sec*-butylpyridine *(17)* in over 90% yield. For example, (*S*)-(+)-*(17)* was obtained in 96% enantiomeric excess.

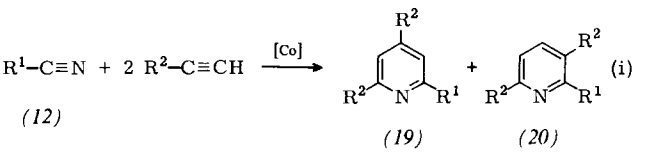
However, the catalytic reaction does not yield lutidines selectively: Table 4 shows that the yields of lutidines formed catalytically according to eq. (h) correspond to the statistically expected distribution.

5. Catalytic Synthesis of 2,3,6- and 2,4,6-Trisubstituted Pyridines

A wide field of application of the one-step catalytic synthesis is found in the field of trisubstituted pyridines of types *(19)* and *(20)*. They can be prepared, with high catalyst turnover numbers, according to eq. (i) at *ca.* 130°C using cobalt com-

[*] Addition of more than two molecules of phosphane, arsane, and CO or isocyanide per cobalt atom merely blocks the catalyst.

plexes of type *(4)* or catalysts generated *in situ*, such as *(9)*, *(10)*, *(11)*, or *(15)*.



6. Catalytic Synthesis of Bipyridines

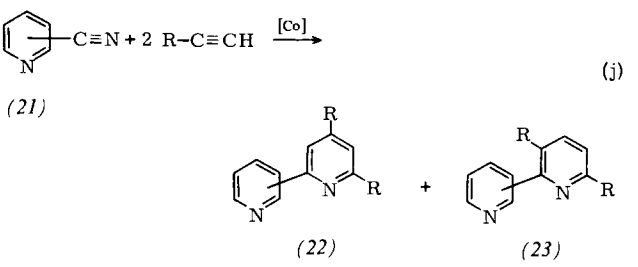
Polynuclear pyridine derivatives can also be synthesized in high yields using cobalt catalysts[24]. Starting from the readily available pyridinecarbonitriles *(21)*, reaction with terminal alkynes leads to the bipyridines *(22)* and *(23)* [eq. (j)].

Table 5. Trisubstituted pyridines *(19)* and *(20)* obtained according to eq. (i) [catalyst *(4)*, *(9)*—*(11)*, or *(15)*; reaction temperature *ca.* 130°C; work-up by distillation].

R^1	R^2	Isomeric ratio [a] *(19)*	*(20)*	Separation or identification	Yield [%] [b]	B.p. [°C/torr] [c]	M.p. [°C] [d]	M^+ (*m/e*)	Products known according to ref. *(19)*	*(20)*
CH_3	CH_3	61	39	GC	71	174–179/760		121	[45, 46, 80–82, 88–93]	[45, 46, 80–82, 84]
CH_3	n-C_5H_{11}	69	31	GC	58	84–96/10^{-4}		233		
CH_3	C_6H_5	80	20	^{1}H-NMR	62	170–190/10^{-4}	56	245	[94, 95]	
C_2H_5	CH_3	75	25	GC ^{1}H-NMR	84	69–73/13		135	[96]	
C_2H_5	C_6H_5	65	35	^{1}H-NMR	55	180–210/10^{-4}		259		
n-C_5H_{11}	CH_3	60	40	GC	62	47–61/10^{-4}				
$CH=CH_2$	CH_3	71	29	^{1}H-NMR	85	81/12		133	[97–99]	
C_6H_5	CH_3	68	32	GC	54	58–95/10^{-4}		183		
C_6H_5	C_6H_5	77	23	GC	51		138	307	[68, 87, 100, 101]	

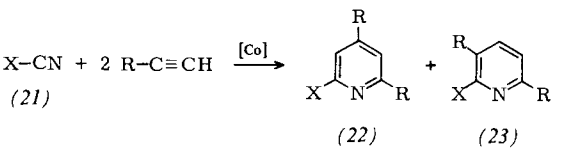
[a] On ^{1}H-NMR spectroscopic analysis, the isomeric ratio was determined from the intensity ratios of the signals characteristic for each of the structures. [b] Based on reacted alkyne, not optimized. [c] B.p. of mixture of isomers. [d] M.p. of mixture of isomers; purification by acid-base separation.

The catalytic reaction of terminal alkynes always leads to two isomeric pyridine derivatives: the symmetrically substituted type *(19)* is formed as the major product, while the asymmetric type *(20)* is formed in about 30% relative yield. The substituents R^1 and R^2 can be varied within wide limits and combined at will. The nitrile component may be an alkyl derivative of any length or an aryl compound. In this last case phenylpyridines are formed in a single step. This appears particularly remarkable because no single, general method was previously available for the production of phenylpyridines (cf., *e.g.*, [97]). The results obtained so far are summarized in Table 5.



Use of acetylene as the alkyne component gives the respective parent compound, *e.g.* 2,2′-bipyridine. Up to 350 catalytic cycles [eq. (j)] can be performed on a cobalt compound such

Table 6. Bipyridine derivatives *(22)* and *(23)* obtained according to eq. (j) [catalyst, *e.g.*, *(5)*; reaction temperature 120–130°C; almost complete conversion; work-up by distillation].



X	R	Isomeric ratio [a] *(22)* : *(23)*	Yield [%]	Major fraction B.p. [°C/torr]	n_D^{20}	M^+ (*m/e*)	Products known according to ref.
2-Pyridyl	H		95	273/760		156	[102–123]
	CH_3	72 : 28	91	122/10^{-3}	1.589	184	
	C_6H_5	60 : 31	79	120/10^{-4}		308	
3-Pyridyl	H		92	286/760		156	[105–109]
	CH_3	62 : 38	94	123/10^{-3}	1.589	184	
4-Pyridyl	H		93	281/760		156	[109, 124, 125]
	CH_3	54 : 46	90	125/10^{-3}	1.589	184	

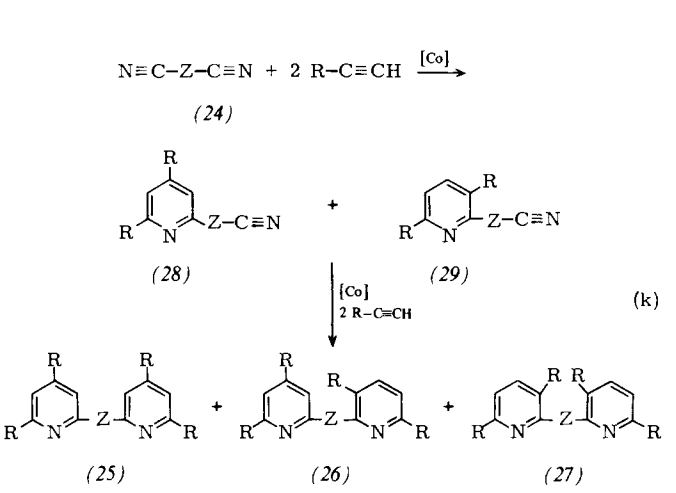
[a] Determined by ^{1}H-NMR spectroscopy.

as *(5)*. Substituted alkynes give two positional isomers, with type *(22)* usually predominating. The bipyridines *(22)* and *(23)* bearing different substituents on the two rings, which were inaccessible by classical methods, could be of interest for the synthesis of transition metal bipyridine complexes. Some typical examples are shown in Table 6.

Particular industrial interest attaches to the new synthesis of 2,2'-bipyridines. The quaternization product of bipyridine and 1,2-dibromoethane is a commonly used herbicide.

7. Catalytic Reaction of α,ω-Dinitriles with Alkynes

The procedure corresponding to eq. (j) is also applicable to α,ω-dinitriles *(24)*. The bifunctional starting materials *(24)*



(k)

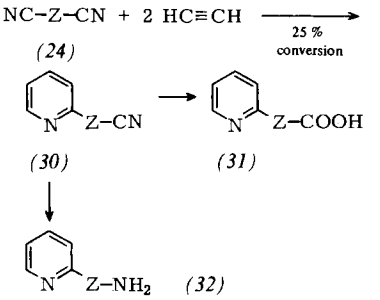
Table 7. 2,2'-Oligomethylenedipyridines and 2,2'-(1,4-phenylene)dipyridine *(25)–(27)* [catalyst, *e.g.*, *(5)*; reaction temperature 140–150 °C; almost complete conversion; work-up by distillation].

Z	R	Yield [%]	Major fraction B. p. [°C/torr]	n_D^{20}	M^+ (*m/e*)	Products known according to ref.
—CH_2—	CH_3	72 [a]	90/10^{-3}		170	
	C_6H_5	70 [a]	160/10^{-4}		474	
—$(CH_2)_2$—	H	97	105–110/0.5	1.578	184	[126, 127]
	CH_3	94	143–146/0.1		240	[126]
	C_6H_5	83	170/10^{-4}		488	
—$(CH_2)_3$—	H	92	135/25		198	[127]
	CH_3	96	155/0.1		254	
—$(CH_2)_4$—	H	98	125/0.2		212	[127]
	CH_3	90	160/0.1		268	
	C_6H_5	86	178/10^{-4}		516	
—$(CH_2)_5$—	H	92	126/10^{-3}		226	[127]
	C_6H_5	81	189/10^{-4}		530	
—$(CH_2)_6$—	H	97	128/10^{-3}		240	[127]
	CH_3	92	137/10^{-4}		296	
—$(CH_2)_7$—	H	92	138/10^{-3}	1.536	254	[127]
	CH_3	94	160/10^{-3}		310	
	C_6H_5	79	230/10^{-4}		558	
—$(CH_2)_8$—	H	90	100/10^{-4}		268	[127]
	CH_3	96	122/10^{-4}		324	
1,4-C_6H_4	H	94	230/2·10^{-3}		232	[128]

[a] 4-Amino-2,6-bis(cyanomethyl)-5-pyrimidinecarbonitrile is formed as a by-product in a yield of preparative interest.

containing any number of bridging members Z afford the bis(2-pyridyl) derivatives *(25)*, *(26)*, and *(27)*. The reaction proceeds stepwise: in the first step the monopyridyl derivatives *(28)* and *(29)* are formed; this is followed by reaction of the cyano group with further alkyne [eq. (k)].

As shown by Table 7, the otherwise rather inaccessible or unknown oligomethylenepyridines *(25)*—*(27)* can be prepared in good yield, without about 450 cyclization steps being achieved per cobalt atom of the catalysts *(5)* or *(14)*.



(l)

Table 8. ω-(2-Pyridyl)alkanonitriles *(28)* and *(29)* obtained according to eq. (k) at 25 % conversion of dinitrile *(24)* [catalyst, *e.g.* *(5)*; reaction temperature 80–90 °C; work-up by distillation].

Z	R	Isomeric ratio [a] *(28)*	*(29)*	Yield [%]	Major fraction B. p. [°C/torr] [b]	n_D^{20}	M^+ (*m/e*)
—$(CH_2)_2$—	CH_3	72	28	79	96–98/2	1.518	160
—$(CH_2)_3$—	CH_3	70	30	81	95–97/1	1.519	174
—$(CH_2)_4$—	CH_3	71	29	89	135–138/0.4	1.489	188
—$(CH_2)_6$—	CH_3	72	28	83	142–145/0.5	1.484	216
—$(CH_2)_8$—	CH_3	77	23	84	150–152/0.2	1.463	244
—CH_2—	C_6H_5	69	31	59	170–185/10^{-4}		270
—$(CH_2)_4$—	C_6H_5	72	28	68	177–196/10^{-4}		312
—CH_2—CH=CH—CH_2—	CH_3	74	26	78	90–99/10^{-4}		186
1,4-C_6H_4	CH_3	62	38	85	110–120/10^{-4}		208

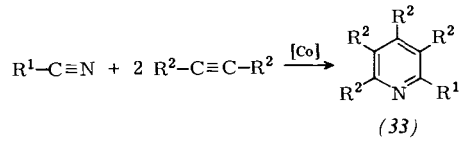
[a] Determined by ^{1}H-NMR spectroscopy. [b] B. p. of mixture of isomers.

If the catalytic reaction of eq. (k) is interrupted after *ca.* 25% of the dinitrile has been consumed then monopyridyl derivatives of type *(30)* may be obtained without difficulty on a preparative scale [eq. (l); cf. Table 8].

As suggested in eq. (l), the cyano compound *(30)* is readily transformed into the acid *(31)* or reduced to the amine *(32)*.

8. Catalytic Synthesis of Pentasubstituted Pyridines; Synthesis of Derivatives with Functional Groups

Pyridine derivatives having a higher degree of substitution can also be prepared catalytically [eq. (m)]. 2-Butyne or diphenylacetylene, for example, reacts with nitriles to give pentasubstituted pyridines *(33)* (Table 9).



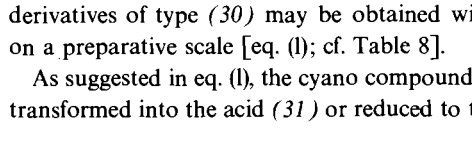
(m)

(33)

$R^1 = CH_3$, C_2H_5 etc.; $R^2 = CH_3$, C_6H_5 etc.

It has become apparent in the course of our studies that cobalt-catalyzed pyridine synthesis is by no means limited to carbonitriles. Even extensive modifications of the cyano components in the pyridine synthesis are tolerated by cobalt catalysts of types *(5)*, *(15)*, and *(4)*. Monomeric cyanamide[*] yields 2-aminopyridines *(34)* according to eq. (n) with the catalyst systems mentioned.

Aminopyridines of type *(34)* (Table 9) possess considerable preparative interest but can usually only be prepared by substitution of ready-made pyridine rings (cf. ref. [130]), in several steps.



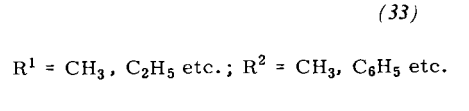
(n)

R = H, Alkyl, Aryl

(34)

A catalytic cyclotrimerization reaction, using a modification of eq. (m), leads to pyridine rings having ether functions *(36)*. These are useful for pharmaceutical applications (Table 9).

Alkyl thiocyanates can also be used as the cyano component; one-step reactions according to eq. (o) give alkylthiopyridines *(35)* which are otherwise accessible only with difficulty[135][*]. Although most of the Co^I systems are blocked within a few steps by deposition of free sulfur so that true catalysis according to eq. (o) cannot occur, use of catalyst *(5)* in toluene permits synthesis of *ca.* 40 to 50 mol *(35)*/mol *(5)*. Some of these results are compiled in Table 9.



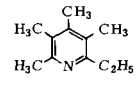
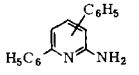
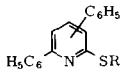
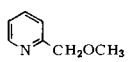
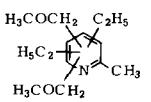
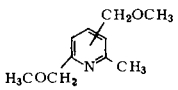
(35) (o)

$R^1 = CH_3$, C_2H_5, $i\text{-}C_3H_7$; $R^2 = C_6H_5$, C_4H_9

Hong and *Yamazaki*[131] recently reported the catalytic reaction of acetylene derivatives with isocyanates and carbodiimides. Phosphane-substituted systems of type *(8)* and cobaltocene served as catalysts.

The reaction of isocyanates and alkynes according to eq. (p) can also be conducted with a similar degree of success

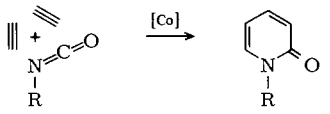
Table 9. Pyridine derivatives of type *(33)* [eq. (m)], *(34)* [eq. (n)], *(35)* [eq. (o)], and *(36)* [modification of eq. (m)] [work-up by distillation].

Product		Yield [%] [a]	B.p. [°C/torr] (M.p. [°C])	M^+ (*m/e*)	Product known according to ref.
(33a)		77	57/10^{-1}	163	
(34a)		87	(95) [b, c]	246	
(35a)		78	153–159/10^{-4} [c]	277	
	R = CH_3				
(35c)	R = $i\text{-}C_3H_7$	83	160–167/10^{-4} [c]	291	
(35b)	R = C_2H_5	85	170–178/10^{-4} [c]	305	
(36a)		85	67/12	123	[129]
(36b)		72		181	
(36c)		68 [b, c]		237	

[a] Based on reacted nitrile component, not optimized. [b] Purified by acid-base separation. [c] Isolation of mixture of isomers.

[*] Monomeric cyanamide is available in various grades from Süddeutsche Kalkstickstoffwerke AG, D-8223 Trostberg.

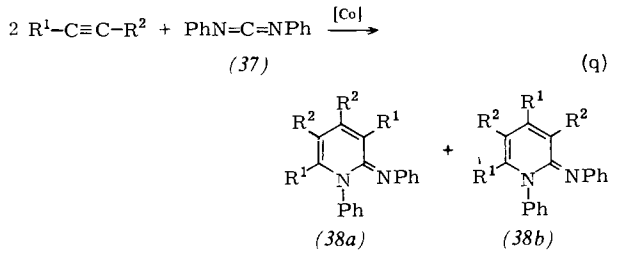
[*] This variant was developed by Dr. *G. S. Natarajan*, Nagpur University, India, 1974—1976 DAAD Guest Scientist at the Max-Planck-Institut für Kohlenforschung.



(p)

using our catalysts *(5)* and *(11)* to give 2-pyridones. About 200 catalytic steps take place per cobalt atom.

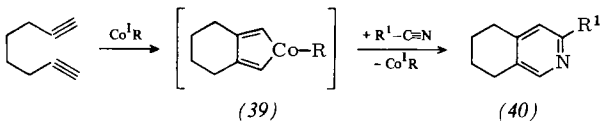
In the presence of complex *(8)* or of cobaltocene, the carbodiimides *(37)* react catalytically to form the imines *(38)* [eq. (q)][131].



(q)

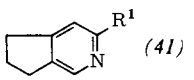
(37) *(38a)* *(38b)*

A highly interesting variation becomes possible by reaction of acetylenes on $CpCo^{I}$(diene) systems *(4)* [eq. (r)]. 1,7-Octadiyne initially gives the non-isolable intermediate *(39)* containing a cyclohexane ring in an intramolecular process. In



(39) *(40)*

(r)



(41)

the presence of an excess of nitrile, a second ring closure takes place at the cobalt and leads to derivatives of tetrahydroisoquinoline *(40)* in *ca.* 60% yield. Compound *(41)* is obtained analogously from 1,6-heptadiyne.

The annelated pyridines *(40)* and *(41)* are also obtained with $CpCo(CO)_2$ as catalyst[132].

9. Mechanism of the Cobalt-Catalyzed Pyridine Synthesis

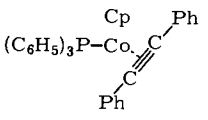
The product formation using catalysts containing the $CpCo^{I}$ group as central moiety, can be rationalized in terms of a double reaction cycle (Fig. 1). The left-hand cycle (bold arrows) represents the principal reaction leading to pyridine as the catalytic reaction product; the right-hand cycle explains the formation of carbocyclic by-products.

Both cycles start with a $CpCo^{I}$ complex *(6)* which initially coordinates an acetylene molecule to form *(42)*. This coordinatively unsaturated species can accept a further molecule of acetylene, under formation of a cobaltacyclopentadiene. This cobalt-containing intermediate, shown enclosed in a box, may be regarded as a junction between the pyridine and benzene cycles.

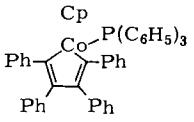
The product-forming step of the catalysis consists in insertion of a third triple bond. In the case of a nitrile molecule (left-hand cycle), the pyridine derivative *(14)* is formed catalytically *via (43)* while coordination of a third acetylene molecule (right-hand cycle) leads catalytically to benzene.

The phosphane-stabilized complexes *(44)*, reported by *Yamazaki et al.* in another context in 1970[133], can serve as model compounds for the intermediates shown in Figure 1.

(44a) can be compared with species *(42)*, while *(44b)* resembles the postulated intermediate *(43)* [cf. also catalyst *(8)*].

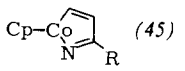


(44a)



(44b)

An intermediate of type *(45)* might be considered as an alternative to the central intermediate shown in Figure 1.



(45)

Results of kinetic studies[134], however, show that the rate of catalytic pyridine formation is independent of the concentration of nitrile in the reaction mixture. If the catalytic pyridine formation were to proceed *via* -containing intermediates of type *(45)*, then high nitrile concentrations would accelerate the catalytic reaction. The available experimental evidence

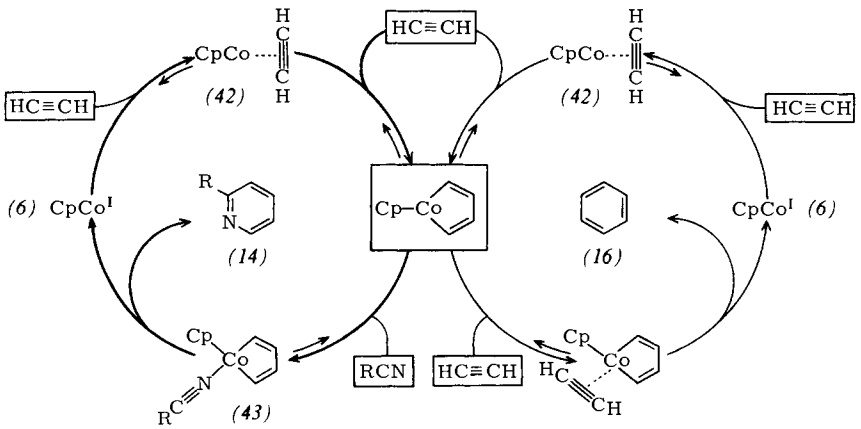


Fig. 1. Cobalt(I)-catalyzed reaction of alkyne and nitrile [cf. eq. (f)].

shows that this is not the case and intermediates of type *(45)* are thus highly unlikely.

Kinetic measurements also revealed that the reaction rates of both catalytic cycles show a quadratic dependence upon the acetylene concentration.

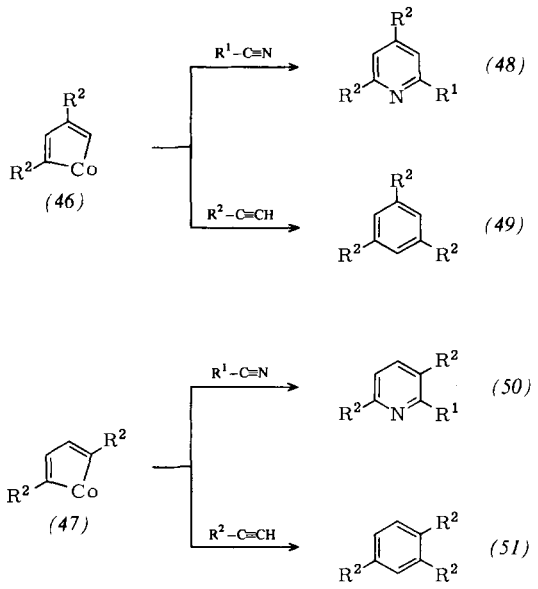
If a large steady-state concentration of acetylene is made available to the central intermediate shown in Figure 1, which is evidently formed in the rate-determining step of the catalysis, then the reaction is increasingly diverted into the right-hand cycle and benzene formation predominates.

Two characteristics of the catalytic reaction course appear to be important:

1) Cyclic alternation of the formal valency between cobalt(I) and cobalt(III);

2) cyclic alternation of the coordination numbers and coordination geometries of the central atom.

The formation of positional isomers in reactions involving terminal alkynes is readily explained by assuming the intermediacy of the cobalt-containing five-membered ring. Intermediate *(46)* results from head-to-tail linkage at cobalt and, after insertion of the third triple bond, affords compounds *(48)* and *(49)* with symmetrical substitution. Intermediate *(47)* results from tail-to-tail linkage of the alkynes to cobalt, and leads to the asymmetrically substituted products *(50)* and *(51)*.

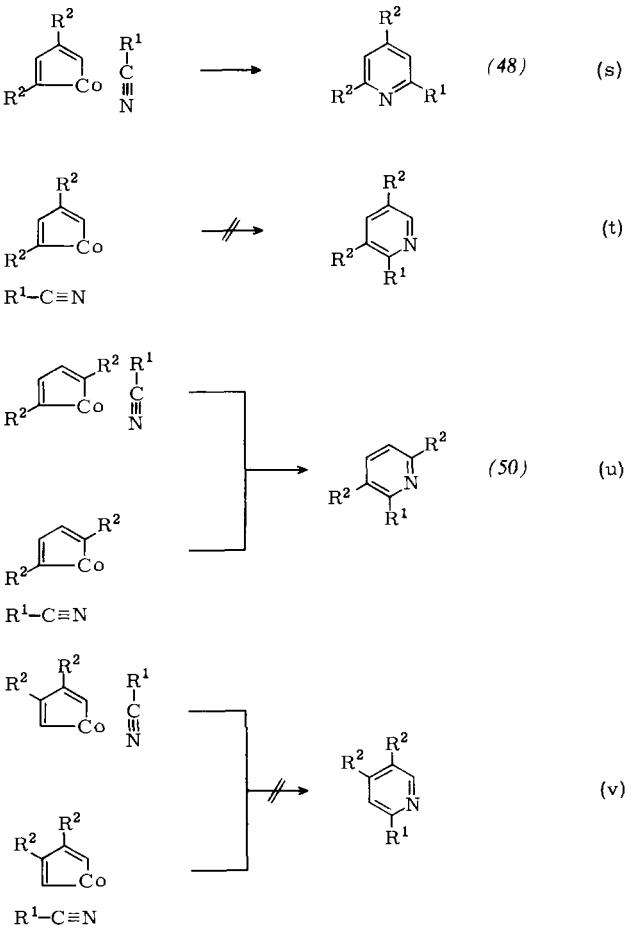


$R^1 = C_2H_5$, $R^2 = CH_3$

The trisubstituted pyridines obtained by cobalt catalysis provide further information about the course of reaction at the cobalt. This is shown schematically in equations (s) to (v).

Insertion of the C≡N triple bond of the nitrile into the CoC bond evidently occurs in such a manner that the nitrogen atom initially interacts with the cobalt. This is supported in particular by the findings corresponding to eq. (s).

Products which would arise from intermediates with a vicinal substitution pattern (head-to-head linkage of the acetylenes [eq. (v)]) are not formed.



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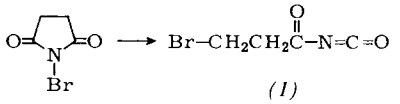
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More about π- and σ-Succinimidyl Radicals: Ring Opening Reactions[**]

By *Philip S. Skell, James C. Day,* and *Joseph P. Slanga*[*]

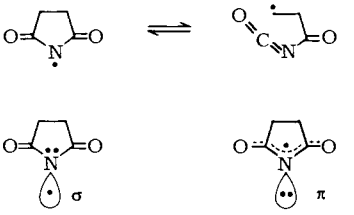
Until recently[1-3] the reactions of the succinimidyl radical were virtually unknown, or unrecognized, with the exception of its intermediacy in the rearrangement of *N*-bromosuccinimide (NBS) to β-bromopropionyl isocyanate *(1)*, a reaction which had defied understanding[4].



NBS

(1)

The various parts of the puzzle are now accommodated by the hypothesis that succinimidyl radical undergoes rapid and reversible ring cleavage, and that trapping of the open-chain form leads to the β-halopropionyl isocyanate. Of the two types of succinimidyl radicals which have been recognized[2], the σ type undergoes this cleavage reaction while the π type does not.



The assemblage of experimental results which are to be accommodated by this hypothesis are summarized below.

1) Irradiation (or heating, with benzoyl peroxide initiation) in the presence of alkenes results in 25–90% yields of acyl isocyanate *(1)* for *N*-bromo- (NBS) and *N*-iodosuccinimide (NIS); no isocyanate is formed if *N*-chlorosuccinimide (NCS) is used, or any of the *N*-halophthalimides or *N*-haloglutarimides, despite the fact that the same H-abstractions, additions to alkenes, and additions to arenes are observed as for NBS and NIS.

2) Within large limits the above results are insensitive to changes in olefin concentrations (see also [4b]).

3) In the presence of large concentrations of alkenes (or benzene) no isocyanates are obtained; the succinimidyl moieties are found as succinimide (H-abstraction) and in 1,2-adducts to the olefin (or benzene)[3].

4) In the presence of Br_2 or I_2 no isocyanates are formed; only H-abstractions occur, among them abstractions which cannot be attributed to $Br^{\bullet}$ or $I^{\bullet}$.

5) One or more alkyl substituents on NBS have only a small effect on its reactivity in the presence of alkenes, as determined in competition reactions in which the rate of disappearance of the NBS derivatives is monitored[5]. However, the product is 100% isocyanate when the alkyl-substituted NBS is used, whereas under the same circumstances NBS itself gives 25–60% yields of isocyanate (and succinimide arising by H-abstraction). In the presence of alkenes the succinimidyl radicals are exclusively σ type.

6) On the other hand, in the reaction of *N*-bromo-3,3-dimethylsuccinimide with neopentane in CH_2Cl_2 in the presence of Br_2, no isocyanate formation is observed (absence of 2230 cm^{-1} band). The reaction products are neopentyl bromide, $BrCHCl_2$, and 3,3-dimethylsuccinimide. In the presence of Br_2 the succinimidyl intermediate is exclusively of π type. There seems to be no significant interconversion of σ and π types under these reaction conditions.

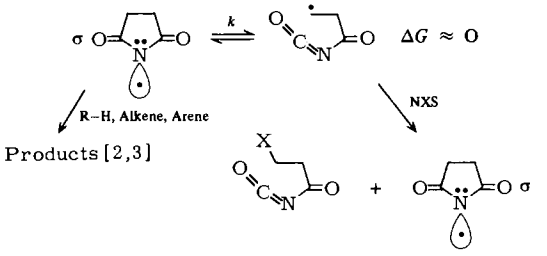
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7) The percentage of NBS converted into isocyanate decreases with decreasing concentration of NBS, without affecting the relative rates of the competing processes.

In the presence of halogens the succinimidyl generation step ($X^{\bullet} + NXS$) is almost thermoneutral and thus can produce only the ground state, π radical[2], which does not correlate[6] with the ground state of the open-chain radical. On addition of alkene but no halogen, the alkene functions as a halogen scavenger and thus makes possible the generation ($R^{\bullet} + NXS$) of the σ radical[2], which does correlate[6] with the ground state of the open-chain radical. Thus, in the presence of halogen, π-succinimidyl radicals arise which can abstract hydrogen but do not form isocyanates; in the presence of alkenes, σ radicals are produced, leading to competition between ring opening and hydrogen abstraction.

σ-Succinimidyl is postulated to undergo a rapid, reversible ring-opening reaction; thus it is possible to explain all the observations.



Reactions of the σ-succinimidyl radical in H-abstraction and additions to alkenes or arenes are very fast, the rates being almost encounter-controlled[3]. NBS and NIS can trap the open-chain radical, the much less reactive NCS cannot; thus there is no ring-opened product from NCS. The rate constant k must exceed $10^8\,s^{-1}$.

With one or more alkyl substituents on the ring, open chain secondary and tertiary radicals can arise, which are more stable than the cyclic radical. Therefore, formation of open-chain radical is rapid; isocyanates are produced exclusively. The ring-opening rates k probably approach $10^{10}\,s^{-1}$, since H-abstractions by the σ-succinimidyl forms are not observed. On the other hand, in the presence of Br_2, the *N*-bromo-3,3-dimethylsuccinimide yields a π-succinimidyl which cannot undergo ring opening, and thus only H-abstractions are observed.

A critical test of this rationalization was obtained by demonstrating that in the NCS reactions (presence of alkene) in which succinimide is the only product (no isocyanate is observed), some of succinimidyl radicals must spend some time in the open chain form before they abstract a hydrogen atom to form succinimide.

cis-3,4-Dideuteriosuccinimide was synthesized by reaction of maleimide with D_2 over a palladium catalyst[7]; this was converted into $[D_2]$-NCS and $[D_2]$-NBS. Reaction of the $[D_2]$-NBS with neopentane in the presence of Br_2 (CH_2Cl_2 solvent) resulted in formation of pure *cis* compound, identical (IR) with starting material. These are conditions for intermediacy of the π-succinimidyl[2]. On the other hand, reaction of $[D_2]$-NCS in the presence of alkene produced analytically pure dideuteriosuccinimide[8], which is 70% *cis* and 30% *trans* (IR). These are conditions for the intermediacy of σ-succinimidyl[2], and the experiment demonstrates the intermediacy of an open-chain species in the conversion of NCS into succinimide, an open-chain intermediate which is not trapped by NCS to produce an isocyanate, but instead, closes the ring and then abstracts hydrogen.

These new results add force to the earlier suggestion that thermal chain reactions involving succinimidyl radicals can involve either π or σ states of the radical.

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(1), 18926-24-4; NBS, 128-08-5; *cis*-3,4-dideuteriosuccinimide, 66633-57-6

[1] *J. G. Traynham, Y. S. Lee*, J. Am. Chem. Soc. *96*, 3590 (1974); *J. C. Day, M. J. Lindstrom, P. S. Skell, ibid. 96*, 5616 (1974); *P. S. Skell, J. C. Day, ibid.*, in press; Acc. Chem. Res., in press; imidyl radicals are H-abstractors of low discrimination; they add readily to alkenes and arenes.
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[8] The 3,4-dideuteriosuccinimides were analyzed by mass spectra (parent ion, $m/e = 101$) and IR. The intensity of the CHD bands at 700 and 510 cm^{-1} decreases by 70% on reaction of $[D_2]$-NCS in the presence of alkenes while new bands appear at 730 and 525 cm^{-1}.

Methylenesulfur Tetrafluoride $H_2C{=}SF_4$[**]

By *Gert Kleemann* and *Konrad Seppelt*[*]

We have now synthesized the carbon analog of $HO{-}SF_5$[1] and $H_2N{-}SF_5$[2], namely $H_3C{-}SF_5$, in the following manner: Sulfur chloride pentafluoride reacts in the usual way[3] with ketene to give $SF_5CH_2{-}COCl$, which by hydrolysis is converted into the acid $SF_5CH_2{-}COOH$. Hunsdiecker degradation of the silver salt of this acid yields $SF_5{-}CH_2Br$, which in turn is reduced to the desired compound $H_3C{-}SF_5$.

$$SF_4 + Cl_2 + CsF \xrightarrow{250\,^{\circ}C} SF_5Cl + CsCl$$

$$SF_5Cl + CH_2{=}C{=}O \xrightarrow{CFCl_3,\ 20\,^{\circ}C} SF_5{-}CH_2{-}COCl$$
B.p. 48 °C/130 mbar

$$SF_5{-}CH_2{-}COCl \xrightarrow[-HCl]{H_2O} SF_5{-}CH_2{-}COOH$$
Subl. 40 °C/0.5 mbar, M.p. 64 °C

$$SF_5{-}CH_2{-}COOH \xrightarrow[-CO_2,\ -H_2O]{Ag_2CO_3} SF_5{-}CH_2{-}COO^{-}Ag^{+}$$

$$SF_5{-}CH_2{-}COO^{-}Ag^{+} + Br_2 \xrightarrow{CFCl_3} CO_2 + AgBr + SF_5{-}CH_2Br$$
B.p. 75 °C

$$SF_5{-}CH_2Br \xrightarrow{Zn/HCl} H_3C{-}SF_5$$
B.p. 26 °C, M.p. −11.5 °C

Methylsulfur pentafluoride, which is colorless and stable towards hydrolysis, was characterized like all the precursors by elemental analysis and on the basis of mass, IR, and NMR spectral data. The ^{19}F-NMR spectrum of $H_3C{-}SF_5$ shows a typical AB_4 pattern, the B_4 resonances appear as a quartet ($J_{HF} = 9.8$ Hz), and the ^1H-NMR signal of the methyl group ($\delta_H = 3.4$) is split into a quintet.

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In contrast to H_2NSF_5 and $HOSF_5$, H_3CSF_5 shows no tendency to eliminate HF at room temperature. The product of such an elimination is obtainable, however, by another method: the bromine-lithium exchange in SF_5—CH_2Br leads to spontaneous loss of LiF and formation of $H_2C{=}SF_4$.

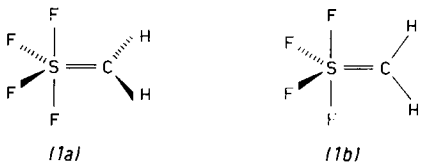
$$SF_5{-}CH_2Br + n\text{-}C_4H_9Li \xrightarrow{-110\,^\circ C} SF_5{-}CH_2Li + n\text{-}C_4H_9Br$$

$$SF_5{-}CH_2Li \xrightarrow{-70\,^\circ C} LiF + H_2C{=}SF_4$$

B. p. −19 °C, m. p. −140 °C

Methylenesulfur tetrafluoride is a colorless gas, stable up to at least 100 °C. Its composition was confirmed by its mass spectrum [70 eV: $m/e = 122$ ($CH_2SF_4^+$, 100%), 103 ($CH_2SF_3^+$, 21%), 102 ($CHSF_3^+$, 3%), 89 (SF_3^+, 65%), 84 ($CH_2SF_2^+$, 3%), and further fragments] and by Dumas vapor density determination [$M_{r,exp} = 121$].

$H_2C{=}SF_4$ is not an ylide. Its ^1H- and ^{13}C-NMR data ($\delta_c = 43.9$) differ markedly from those of typical ylides such as $H_2\overset{\ominus}{C}{-}\overset{\oplus}{P}R_3$[4]. The relatively low reactivity of this species is also consistent with the double bond formulation. The complex ^{19}F and ^1H nuclear magnetic resonances (Fig. 1) can be interpreted only in terms of a $A_2BB'XX'$ spectrum [−150 °C: $\delta_{F(A)} = -59.0$, $\delta_{F(B)} = -53.6$, $\delta_H = 2.6$; $J_{AB} = 154.4$, $J_{AX=AX'} = 10.5$, $J_{BX=B'X'} = 9.7$, $J_{BX'=B'X} = 58.1$ Hz].



(1a) (1b)

In the related pentacoordinated species such as PF_5, SOF_4, and $SeOF_4$ the fluorine atoms exchange geometrically nonequivalent sites even at −150 °C. The observed ^{31}P-^{19}F and ^{77}Se-^{19}F coupling constants provide proof of an intramolecular mechanism in PF_5[6] and $SeOF_4$[7], and the same can be assumed for SOF_4 (Berry or turnstile mechanism). Berry pseudorotation in $H_2C{=}SF_4$ leads to the structural transformation *(1a)* → *(1b)* with retention of nonequivalency of the fluorine atoms, unlike the situation in the case of $O{=}SF_4$. As in PF_5, SOF_4 and other molecules such a rearrangement can take place even at low temperatures. A striking change in the δ_F value with rising temperature is probably indicative of a rapid and reversible equilibrium of *(1a)* and *(1b)* in terms of a Berry mechanism.

The turnstile rotation would make all fluorine atoms magnetically equal, but this is not observed. Magnetic equality could theoretically also be achieved by a Berry mechanism of the fluorine atoms and a synchronous torsional motion of the

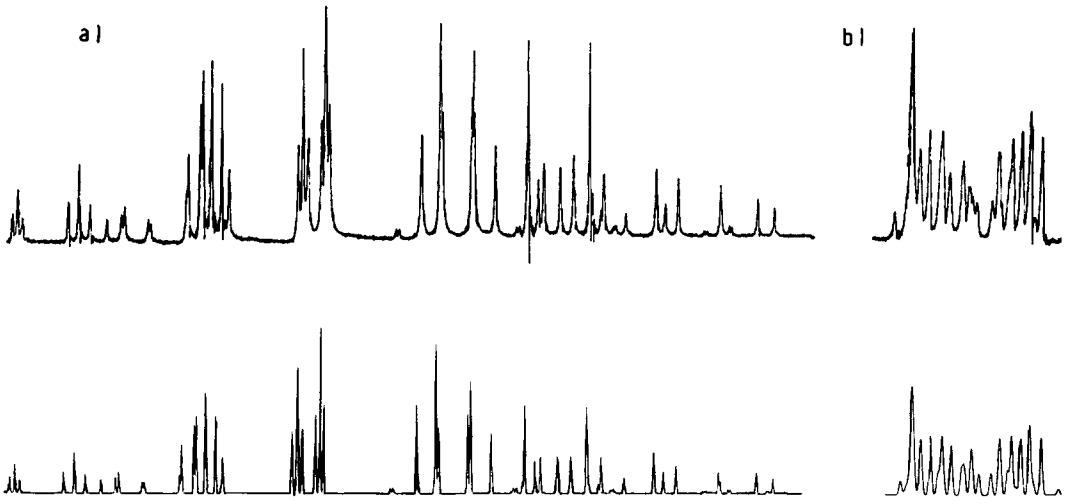
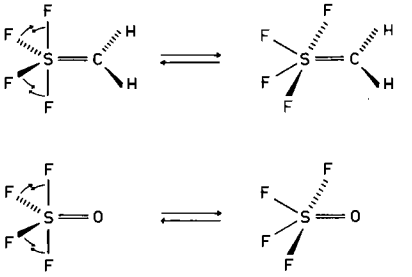


Fig. 1. a) ^{19}F- and b) ^1H-NMR spectrum of $H_2C{=}SF_4$ (56.4 and 60 MHz, respectively): above, experimental; below, simulated as $A_2BB'XX'$ spectrum.

This means that the methylene group is coplanar with a pair of fluorine atoms (BB'XX'); free rotation about the S=C axis is not observed. Since the spectra do not change in character up to +100 °C, the torsional barrier (double bonding contribution) is estimated to be over 25 kcal/mol. In the IR (gas) spectrum and in the Raman (liquid) spectrum a strong band is observed at 1170 cm^{-1} that is assigned to the S=C stretching vibration. This indicates a high bond order (1.9 according to *Siebert*[5], in contrast to 1.2 in the case of phosphorus ylides).

As yet it is uncertain whether the H atoms lie in a plane with the equatorial [*(1a)*] or the axial F atoms [*(1b)*]. For the double bond, a sulfur orbital of the type $3d_{xy}$ or $3d_{xz}$ (x = S=C axis) is conceivable. We hope to clarify this problem with the aid of theoretical calculations and, experimentally, on the basis of electron diffraction, microwave spectra, and crystal structures.



methylene group, but this is impossible because of the double bond.

The new methylene compound has been observed to undergo a number of reactions analogous to those of the carbenes, *e.g.*

$$CH_2{=}SF_4 \xrightarrow{h\nu} SF_4 + {}^1\!/_2\,CH_2{=}CH_2$$

$$CH_2{=}SF_4 \xrightarrow{Br_2} SF_4 + CH_2Br_2$$

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CAS Registry numbers:
SF_5Cl, 13780-57-9; $CH_2{=}C{=}O$, 463-51-4; $SF_5{-}CH_2{-}COCl$, 2353-88-0; $SF_5{-}CH_2{-}COOH$, 66808-47-7; $SF_5{-}CH_2{-}COO^-Ag^+$, 66808-46-6; $SF_5{-}CH_2Br$, 66793-27-9; $H_3C{-}SF_5$, 753-79-7; $SF_5{-}CH_2Li$, 66793-26-8; $H_2C{=}SF_4$, 66793-25-7

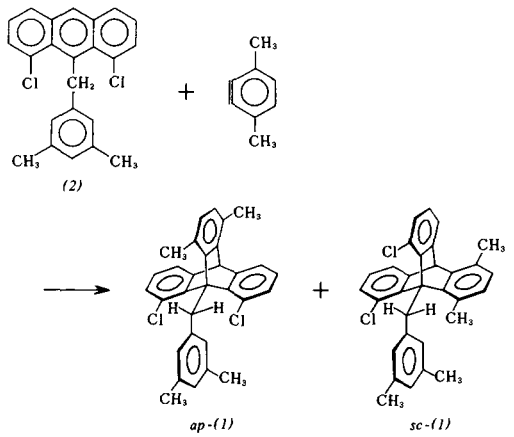
[1] *K. Seppelt*, Z. Anorg. Allg. Chem. *428*, 35 (1977).
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[6] *R. S. Berry*, J. Chem. Phys. *32*, 933 (1960).
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8,13-Dichloro-1,4-dimethyl-9-(3,5-dimethylbenzyl)triptycene: Atropisomerism about a $C_{sp^3}{-}CH_2$ Bond[1]

By *Gaku Yamamoto* and *Michinori Ōki*[*]

Triptycene derivatives carrying a tertiary alkyl group at the bridgehead (C-9) are known to exist as stable rotational isomers, *i.e.* atropisomers, with barriers to rotation of more than 30 kcal/mol[2, 3]. The rotational barriers lower considerably when the bridgehead substituent is a primary or secondary alkyl group[4]. While 9-benzyltriptycenes carrying one *peri*-substituent exhibit barriers to rotation of *ca.* 13 kcal/mol, those carrying two *peri*-substituents show barriers of *ca.* 18 kcal/mol[4a]. It was reasonable therefore to expect that 9-benzyltriptycenes with three *peri*-substituents would have even higher barriers to rotation.

We have now found that introduction of three *peri*-substituents raises the barrier to such an extent that atropisomerism about the $C_9{-}CH_2$ bond is realized in 8,13-dichloro-1,4-dimethyl-9-(3,5-dimethylbenzyl)triptycene *(1)*.



sc-(1) is shown in the *Msc* form.

1,8-Dichloro-9-(3,5-dimethylbenzyl)anthracene *(2)* (m.p. 196—197 °C) was synthesized by addition of 3,5-dimethylbenzylmagnesium chloride to 1,8-dichloroanthrone[5] and subsequent dehydration with thionyl chloride/pyridine[6]. Reaction of *(2)* with 3,6-dimethylbenzyne generated *in situ* from 3,6-dimethylanthranilic acid and isoamyl nitrite in boiling dichloromethane afforded a mixture in which the ratio of *ap-(1)* to *sc-(1)* was about 9:1. Thus a pure sample of *ap-(1)*[7, 8] (m.p. > 300 °C) could be obtained by rough chromatography on alumina followed by recrystallization of the isomer mixture from chloroform/ethanol. Heating a solution of *ap-(1)* in benzene at 80 °C for 5 h gave an equilibrium mixture [*ap-(1)* : *sc-(1)* = 1 : 2], which was chromatographed on alumina (benzene/hexane 1:5), to give a pure sample of *sc-(1)*[7, 9] (m.p. > 300 °C). Assignment of the stereochemistry of each atropisomer followed from the ^{1}H-NMR spectral pattern of the methylene protons: the *ap* isomer shows a singlet, whereas the *sc* isomer shows an AB quartet.

The *ap*/*sc*-isomer ratio of 9 : 1 is consistent with our previous findings that the Diels-Alder reaction of 9-substituted anthracenes proceeds preferentially in a conformation where the bulkiest group at the α-carbon in position 9 occupies an anti-periplanar arrangement to the entering dienophile in the transition state and thus such an atropisomer predominates[3, 10]. The steric requirement is apparently the origin of the kinetic control of the products.

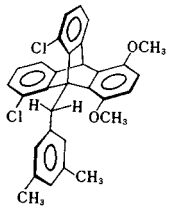
Table 1. Kinetic data for the isomerization of *(1)* in $CDCl_3$.

ap-(1) $\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$ (±)-*sc-(1)* $\quad K = k_1/k_{-1}$

T [°C]	$k_1 \times 10^5$ (s^{-1})	$\Delta G^{\neq}$ [kcal/mol]	K
69	111	24.7_4	2.0
61	42.4	24.7_8	2.0
54	17.1	24.8_4	2.0
48	8.35	24.8_3	2.0

$\Delta H^{\neq} = 27.0$ kcal/mol; $\Delta S^{\neq} \approx +6.6$ cal K^{-1} mol^{-1}.

Kinetic data for the *ap-(1)* ⇌ *sc-(1)* interconversion in $CDCl_3$ were obtained by following the change in relative signal intensities in ^{1}H-NMR spectra at 48—69 °C (Table 1). The equilibrium constant $K = 2.0$ was invariant throughout the temperature range examined.



(3)

The size of the *peri*-substituent seems important in determining the barrier. 8,13-Dichloro-1,4-dimethoxy-9-(3,5-dimethylbenzyl)triptycene *(3)*[7, 11] (m.p. 277—278 °C) showed the coalescence phenomenon of an AB quartet due to the benzyl methylene protons at 167 °C[12]. The free energy of activation for the interconversion of (+)-*sc-(3)* ⇌ (−)-*sc-(3)* at this temperature is calculated to be 22 kcal/mol.

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CAS Registry numbers:
ap-(1), 66808-35-3; *sc-(1)*, 66770-05-6; *(2)*, 66770-04-5; *sc-(3)*, 66770-03-4; 1,4-dimethyldehydrobenzene, 59309-68-1

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[1] Restricted Rotation Involving the Tetrahedral Carbon, Part 22.—Part 21: *S. Otsuka, H. Kihara, T. Mitsuhashi, M. Ōki*, Chem. Lett. *1978*, 475.
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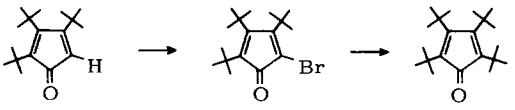
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[7] The 3,5-dimethylbenzyl group in these compounds showed evidence for restricted rotation about the C_{ar}—CH_2 bond: both the methyl groups and the *o*-H atoms became nonequivalent at low temperatures. Coalescence temperatures were about 50°C and the barriers *ca.* 16 kcal/mol.
[8] ^{1}H-NMR ($CDCl_3$, −20°C): δ = 1.87 (3H, s, *m*-CH_3), 2.38 (3H, s, *m*-CH_3), 2.42 (3H, s, 4-CH_3), 2.85 (3H, s, 1-CH_3), 5.43 (2H, s, CH_2), 5.62 (1H, s, 10-H), and 6.1—7.5 (11H, m, aromatic).
[9] ^{1}H-NMR ($CDCl_3$, −20°C): δ = 1.84 (3H, s, *m*-CH_3), 2.18 (3H, s, 1-CH_3), 2.39 (3H, s, *m*-CH_3), 2.58 (3H, s, 4-CH_3), 5.21 and 5.65 (2H, AB-q, J = 18 Hz, CH_2), 5.59 (1H, s, 10-H), and 6.0—7.5 (11H, m, aromatic).
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[11] ^{1}H-NMR ($CDCl_3$, −20°C): δ = 1.88 (3H, s, *m*-CH_3), 2.39 (3H, s, *m*-CH_3), 2.88 (3H, s, 1-OCH_3), 3.86 (3H, s, 4-OCH_3), 5.31 and 5.54 (2H, AB-q, J = 18 Hz, CH_2), 5.89 (1H, s, 10-H), and 6.2—7.5 (11H, m, aromatic).
[12] No sign of the existence of an *ap* form was found, probably due to the steric effect which makes the *ap* form unstable relative to *sc* forms. Thus the rate process observed by the NMR spectra is assumed to be a (+)-*sc* ⇌ (−)-*sc* interconversion.

Tetra-*tert*-butylcyclopentadienone[1]

By *Günther Maier* and *Stephan Pfriem*[*]

While searching for precursors for the photochemical synthesis of tetra-*tert*-butyl-cyclobutadiene and/or -tetrahedrane[2] our choice fell upon tetra-*tert*-butylcyclopentadienone *(3)*. By systematic exploitation of the "antiaromatic"-type reactivity characteristic of the cyclopentadienone ring system, it proves possible to obtain this first example of a compound having four adjacent *tert*-butyl groups in an eclipsed arrangement.

Action of bromine on the tri-*tert*-butyl derivative *(1)*[3] led, in spite of steric hindrance, to a dibromide which readily eliminates hydrogen bromide on treatment with potassium hydroxide to form the bromo dienone *(2)*. Replacement of the halogen in *(2)* by the alkyl group of *tert*-butyllithium is possible only under "forbidden" conditions, *i.e.* in 1,2-dimethoxyethane at room temperature (−50°C should not



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

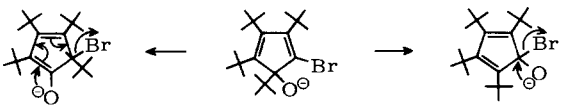
really be exceeded if reaction of the alkyllithium with solvent is to be avoided[4]).

The spectroscopic data of *(2)* and *(3)* are listed in Table 1. Bromination of *(1)* is observed to give first the 2,5-dibromo derivative *(4)* [^{1}H-NMR ($CDCl_3$): δ = 4.88 (ring H), 1.58, 1.50, 1.38; ^{13}C-NMR ([D_6]-benzene): ring C atoms at δ = 200.40, 159.22, 144.04, 84.34, 52.19; IR (CCl_4): 1750 cm^{-1}] which rearranges in solution to the α,β-unsaturated isomer *(5)* [^{1}H-NMR ($CDCl_3$): δ = 4.68 (ring H), 1.60, 1.47, 1.18; ^{13}C-NMR (C_6D_6): ring C atoms at δ = 197.80, 171.21, 149.10, 82.70, 61.90; IR (CCl_4): 1710 cm^{-1}]. Whether the bromine atoms in *(4)* and *(5)* are *cis* or *trans* has not been established.



(4) *(5)*

The unusual reaction conditions for the step *(2)* → *(3)* have their reason in the inability of the primary addition product *(7)* to eliminate a bromide ion. In a preceding step, it must undergo either a 1,5 shift of a *tert*-butyl group [*(7)* → *(6)*]—this is favored by enolate formation in *(6)*[5]—



(6) *(7)* *(8)*

or an oxygen migration [*(7)* → *(8)*]. However, such reactions require higher temperatures than are normally used in reactions with *tert*-butyllithium. Both *(6)* and *(8)* readily eliminate $Br^{\ominus}$ to give the product *(3)*.

Procedure

(2): To a solution of the dienone *(1)* (3.35 g, 13.5 mmol) in CCl_4 (125 ml) at room temperature is slowly added dropwise a mol. equiv. of a 1.55 M solution of Br_2 in CCl_4. The almost quantitative addition is accompanied by decoloration of the solution. 6 N aqueous potassium hydroxide (150 ml) is added, stirring is continued for 2d at room temperature, and the red CCl_4 phase is separated off, washed with water, and evaporated down after drying with $MgSO_4$. Recrystallization from light petroleum at −35°C affords *(2)* (3.55 g, 80%) as dark red crystals.

(3): To a solution of *(2)* (661 mg, 2.02 mmol) in anhydrous 1,2-dimethoxyethane (125 ml) under N_2 at −10°C is added within 5 min a solution of *tert*-butyllithium (3.07 mmol) in hexane. The mixture is maintained at this temperature for 15 min and stirring then continued at room temperature for 2d. Hydrolysis, extraction into light petroleum, evaporation

Table 1. Properties of *(2)* and *(3)*. The isolated compounds gave correct elemental analyses.

	M. p. [°C]	^{1}H-NMR (δ)	^{13}C-NMR (δ)	IR [cm^{-1}]	UV [nm]	MS [*m/e*]
(2)	108—109	(CCl_4): 1.46, 1.41, 1.30	Ring C atoms ([D_6]-acetone): 193.93 (C=O), 179.03, 173.75, 148.17, 113.06 (C—Br)	(KBr): 1701 (C=O), 1561 (C=C)	(cyclohexane): 434 (275), 200 (end absorption, 19200)	328/326 (M^+), 271/269 ($M^+ - C_4H_9$)
(3)	113—115	(CCl_4): 1.34 1.24	Ring C atoms ([D_{12}]-cyclohexane): 197.18 (C=O), 175.77, 143.11	(KBr): 1688 (C=O)	(cyclohexane): 425 (186), 219 (20800)	304 (M^+), 247 ($M^+ - C_4H_9$)

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of solvent, and chromatography of the residue with light petroleum on SiO_2 gives *(3)* (135 mg, 22%) as yellow crystals.

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CAS Registry numbers:
(1), 36319-94-5; *(2)*, 66808-99-9; *(3)*, 66809-00-5; *(4)*, 66809-01-6; *(5)*, 66809-02-7

[1] Small Rings, Part 24. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We are indebted to Ms. *U. Stanior* for experimental assistance.—Part 23: *G. Maier, U. Schäfer, W. Sauer, H. Hartan, R. Matusch, J. F. M. Oth*, Tetrahedron Lett. *1978*, 1837.

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Tetra-*tert*-butyltetrahedrane[1]

By *Günther Maier, Stephan Pfriem, Ulrich Schäfer*, and *Rudolf Matusch*[*]

The synthesis of a tetrahedrane is one of the most attractive challenges yet to be accomplished in organic chemistry. Many setbacks[2] and discouraging theoretical predictions[3] have not deterred us from pursuing this goal.

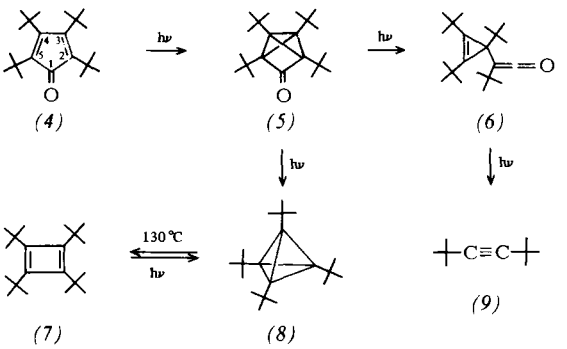
Attempting the isolation of a tetrahedrane *(1)* raises a dilemma: valence-bond isomerization to cyclobutadiene *(3)* and fragmentation into two molecules of acetylene are orbital symmetry forbidden, thus imparting some degree of kinetic stability to *(1)* in spite of its high strain energy [540—574 kJ/mol (129—137 kcal/mol), *i.e.* 88—96 kJ/mol per skeletal bond[3g]]. Nevertheless, *(1)* can also undergo ring opening to the diradical *(2)*. The energy barrier of this reaction path decides whether a tetrahedrane can be obtained. In the tetra-



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

methyl series there are indications that the bicyclobutanediyl diradical does not undergo ring closure to give the tetrahedrane but instead suffers rupture of the backbone bond to give cyclobutadiene[4a]. Moreover, if it is also borne in mind that the *tert*-butyl groups will considerably lower the thermostability of a C—C bond[5], the prospect of preparing a $(CH_3)_3C$-substituted derivative of *(1)* appears very remote.

Our experimental results are therefore all the more astonishing: tetra-*tert*-butylcyclopentadienone *(4)*[1] exhibits entirely different photochemical behavior from the corresponding compound containing just one *tert*-butyl group less [*(4)*, H in place of *t*Bu at C-2]. While the latter cyclizes to housenone on irradiation with 405-nm light in argon at 10 K[4b], *(4)* does not undergo an analogous reaction (bridge formation between C-2 and C-5). However, if dienone *(4)* isolated in argon is excited by 254-nm light then the IR spectrum shows exclusive criss-cross addition to give the tricyclopentanone *(5)*—the carbonyl absorption of *(4)* diminishes and the double band corresponding to *(5)* appears. On prolonged irradiation, carbon monoxide is evolved (2135 cm^{-1}), and the typical band of ketene *(6)* appears, which is also photolabile and liberates further CO, albeit very slowly (a small amount of *(6)* is still present after 3 weeks).



(4) *(5)* *(6)* *(7)* *(8)* *(9)*

IR spectroscopy is insufficiently specific for identifying the hydrocarbons formed in this way. On GC/MS analysis of the photolytic product evaporated from the cold finger, only di-*tert*-butylacetylene *(9)* can be positively identified. The reaction sequence detected in argon can also be observed by IR spectroscopy in a Rigisolve matrix at −196 °C or in solution between −130 °C and room temperature; the final product contains only little acetylene *(9)* at low temperature but consists almost entirely of that compound under normal conditions.

Truly spectacular results were obtained from a long series of low-temperature ^1H-, and especially ^{13}C-NMR spectra. These measurements, which were indispensable for continuous checks of the irradiation experiments, served not only to optimize the reaction conditions, but also as a guideline in the isolation of the products. Thus the ^1H-NMR signals of *(5)*, *(6)*, and *(9)* appear on irradiation of *(4)* in solution at room temperature. However, if the reaction is carried out at −100 °C in $[D_{10}]$-diethyl ether, an additional signal appears at $\delta = 1.21$. This singlet belongs to a hydrocarbon which can be isolated by chromatography and gives three signals at $\delta = 32.26$, 28.33, and 10.20 in the ^{13}C-NMR spectrum. Such a spectrum is in complete agreement with that expected for tetra-*tert*-butyltetrahedrane *(8)*[6]. In view of the downfield shift due to a *tert*-butyl group ($\Delta\delta \approx 25$) which we have noted in numerous model substances, a value of $\delta = -15$ is calculated for the C atoms in the unsubstituted parent compound *(1)*[7].

The tetrahedrane *(8)* forms colorless crystals which are air-stable. The mass spectrum shows the correct molecular mass (field ionization, $M^+ : m/e = 276.1$), and high resolution confirms the composition $C_{20}H_{36}$ (calc. 276.2815; exp. 276.2814). The compound melts at 135 °C, a property which would make a tetrahedrane structure appear most unlikely if there were not the combined evidence of all the spectroscopic data listed in Table 1[8a]. Final confirmation is expected from an X-ray structure analysis[8b]. Almost equally informative is the thermal behavior of *(8)*[9]: heating of the tetrahedrane in cyclosilane[10] effects quantitative isomerization at 130 °C to give tetra-*tert*-butylcyclobutadiene *(7)*. The colorless solution of *(8)* becomes yellowish orange owing to an absorption maximum at 425 nm ($\varepsilon = 38$) in the spectrum of *(7)*. At the same

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Table 1. Spectroscopic data of compounds *(5)*, *(6)*, and *(8)*.

	^{1}H-NMR ($CDCl_3$) (δ)	^{13}C-NMR ([D_{10}]-Et_2O) (δ, rel. to TMS) p = primary, q = quaternary	IR (Argon) [cm^{-1}]
(5)	1.37 (18H), 1.27 (18H)	188.71 (C=O), 60.58 (q), 33.42 (q), 33.11 (p), 30.99 (p), 30.24 (q), 29.32 (q)	1762, 1743 (C=O)
(6)	1.30 (18H), 1.15 (9H), 0.94 (9H)	206.15 (C=O), 129.16 (C=C), 44.92 (q), 40.77 (q), 39.32 (q), 32.72 (q), 32.03 (p), 31.72 (p), 31.11 (p), 30.60 (q)	2077 (C=C=O)
(8)	1.18 (36H)	32.26 (p), 28.33 (q), 10.20 (q, ring C)	2962 (vs), 2928 (w), 2900 (w), 2865 (w), 1475 (w), 1461 (m), 1451 (w), 1383 (w), 1351 (vs), 1216 (s)

time, the singlet of *(8)* ($\delta = 1.49$, relative to the methylene group of the solvent) disappears from the ^{1}H-NMR spectrum in favor of a new peak at $\delta = 1.50$. The likewise long-sought cyclobutadiene *(7)*[11] shows three signals at $\delta = 152.70$, 30.11 (q), and 28.77 (p) in the ^{13}C-NMR spectrum. Unlike the tetrahedrane *(8)*, compound *(7)* is extremely sensitive to oxygen. Di-*tert*-butylacetylene *(9)* is not formed on heating of *(8)*. Irradiation (> 300 nm) of the cyclobutadiene *(7)* in solution at room temperature or in argon at 10 K regenerates the tetrahedrane.

We interpret the stability of *(8)* in the following way: substitution, especially by alkyl groups, should labilize the tetrahedrane ring skeleton because they favor formation of diradicals of type *(2)*[3a]. However, if all the corners of the tetrahedrane unit are occupied by bulky groups then on lengthening one bond of the ring skeleton of *(8)*, two *tert*-butyl groups tending to increase their mutual separation will be forced back together by the other ones ("corset effect"); a tetrahedral structure permits the four substituents to adopt a regular spherical distribution and hence a maximum mutual separation[12].

Procedure

(8): Tetra-*tert*-butylcyclopentadienone *(4)*[1] (313 mg, 1.03 mmol) in a Rigisolve matrix (35 ml) is irradiated with 254-nm light[13] for 77 h at the temperature of liquid nitrogen in thin quartz tubes. After removal of the solvent and chromatography of the crude orange product on SiO_2 [−5 °C; 85 × 1 cm, pentane/ether (50:1)] the following fractions are successively eluted: tetrahedrane *(8)* (100 mg, 35%), ketene *(6)* (37 mg), and a mixture (65 mg) of starting dienone *(4)* and tricyclopentanone *(5)*. Tetra-*tert*-butyltetrahedrane crystallizes from methanol as colorless feathery needles and after sublimation (40 °C/0.02 bar) melts at 135 °C (dec.).

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(4), 66809-00-5; *(5)*, 66809-03-8; *(6)*, 66809-04-9; *(7)*, 66809-05-0; *(8)*, 66809-06-1; *(9)*, 17530-24-4

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[3] Recent calculations: a) *N. C. Baird, M. J. S. Dewar*, J. Am. Chem. Soc. *89*, 3966 (1967); b) J. Chem. Phys. *50*, 1262 (1969); c) *R. J. Buenker, S. D. Peyerimhoff*, J. Am. Chem. Soc. *91*, 4342 (1969); d) *I. J. Miller*, Tetrahedron *25*, 1349 (1969); e) *N. C. Baird*, Tetrahedron *26*, 2185 (1970); f) *I. J. Miller*, Aust. J. Chem. *24*, 2013 (1971); g) *J. M. Schulman, T. J. Venanzi*, J. Am. Chem. Soc. *96*, 4739 (1974); h) *W. J. Hehre, J. A. Pople*, J. Am. Chem. Soc. *97*, 6941 (1975); i) *M. J. S. Dewar*, Pure Appl. Chem. *44*, 767 (1975); k) *H. Kollmar*, Lecture to GDCh General Meeting, Munich 1977; l) *M. C. Böhm, R. Gleiter*, Tetrahedron Lett. *1978*, 1179.—Professor *Schleyer*'s research group at Erlangen is presently examining the experimental applicability of a new principle (reduction of strain energy of tetrahedrane by H/Li exchange): *G. Rauscher, T. Clark, D. Poppinger, P. v. R. Schleyer*, Angew. Chem. *90*, 306 (1978); Angew. Chem. Int. Ed. Engl. *17*, 276 (1978).

[4] a) *G. Maier, H. P. Reisenauer, H.-A. Freitag*, Tetrahedron Lett. *1978*, 121; b) *G. Maier, U. Schäfer, W. Sauer, H. Hartan, R. Matusch, J. F. M. Oth*, *ibid. 1978*, 1837.

[5] *H.-D. Beckhaus, G. Hellmann, Ch. Rüchardt*, Chem. Ber. *111*, 72 (1978).

[6] Remarkably, the quaternary C atoms of the *tert*-butyl groups appear upfield from the primary C atoms only in *(5)*, *(8)*, and *(9)*. The same also applies to di-*tert*-butylketene ([D_{12}]cyclohexane): $\delta = 201.96$, 51.74, 32.56 (p), 31.51 (q)]. There might be some connection between this jump in chemical shift and the sp-type hybridization of the C atom carrying the *tert*-butyl group.

[7] This value differs significantly from those for the ring atoms in prismane [$\delta = 30.6$; *Th. J. Katz, N. Acton*, J. Am. Chem. Soc. *95*, 2738 (1973)] or cubane [$\delta = 47.3$; *E. W. Della, P. T. Hine, H. K. Patney*, J. Org. Chem. *42*, 2940 (1977)] but fits well into the scheme found for bicyclobutane derivatives [cf. *M. Christl, H.-J. Lüddeke, A. Nagyrevi-Noppel, G. Freitag*, Chem. Ber. *110*, 3745 (1977)].

[8] a) Only end absorption [240 (750), 220 (2750), 200 nm (4800)] is seen in the UV spectrum. The Raman spectrum shows characteristic bands at 2970 (m), 2932 (m), 1459 (m), 1441 (m), 1209 (vs), 919 (s), 828 (vs), 575 (s), and 273 (s) cm^{-1}. Detailed analysis of the vibrational spectra, for which we thank Prof. *K. Dehnicke*, supports the proposed tetrahedrane structure *(8)*.—b) In progress in Prof. *H. Irngartinger*'s laboratory, Heidelberg.

[9] Experiments by *K.-D. Malsch*.

[10] Cyclosilane (Merck): 1,1,3,3,5,5-hexakis(trideuteriomethyl)-1,3,5-trisilacyclohexane.

[11] Small amounts of *(7)* are also formed on irradiation of *(4)* (NMR analysis).

[12] This "all-or-none" principle, according to which only unsubstituted tetrahedrane or derivatives bearing bulky substituents at each corner have a chance of being isolated, is not only operative on formation of *(8)* from *(5)* or *(7)* but also on valence-bond isomerization of *(4)* to *(5)*.

[13] We used photoreactors or plain spiral lamps fitted with low pressure Hg lamps produced by the A. Gräntzel Company, Karlsruhe. Lines below 230 nm were filtered out with Vycor glass.

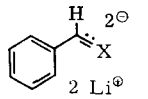
Lithium *ortho*-Lithiobenzyl Alkoxides

By *Norbert Meyer* and *Dieter Seebach*[*]

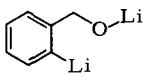
ortho-Lithiation reactions of arenes bearing substituents which contain hetero atoms are known from the early work of *Gilman* and *Wittig*[1]. They have recently been used in numerous directed electrophilic *ortho* substitutions[2].

While attempting to apply the α-deprotonation reaction observed to give *(1)*, X = S, from lithium benzyl thiolate[3], to lithium benzyl alkoxides we have now found that the *ortho*-lithiated derivative *(2)* can be produced in *ca.* 70% yield[4].

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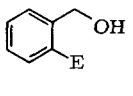


(1), X = S, O

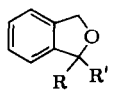


(2)

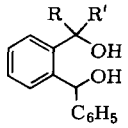
The new reagent *(2)* reacts with electrophiles to form the products *(3)* and *(4a)* compiled in Table 1. The diols *(3d)*—*(3g)* obtained with carbonyl compounds cyclize on treatment with hydrochloric acid/ether[5] to give the dihydroisobenzofurans *(4b)*—*(4e)* (Table 1, bottom).



(3)



(4)



(5)

The physical data of the known compounds [*(3a)*, *(3c)*, *(3f)*, *(3g)*, *(4a)*, *(4d)*, *(4e)*] are in agreement with literature data. Elemental analysis and IR and NMR spectra confirm the structures given. Double metalation of α,α-dideuteriobenzyl alcohol proves that *(2)* is not formed *via (1)*, X = O.

to rise to room temperature, the mixture is poured into dilute sulfuric acid, and the product worked up as usual with ether.

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CAS Registry numbers:
(2), 55274-02-7; *(3a)*, 89-95-2; *(3b)*, 66810-79-5; *(3c)*, 5159-41-1; *(3d)*, 58931-26-3; *(3e)*, 66810-78-4; *(3f)*, 1586-01-2; *(3g)*, 612-14-6; *(4a)*, 87-41-2; *(4b)*, 171-80-2; *(4c)*, 66810-77-3; *(4d)*, 7111-66-2; *(4e)*, 496-14-0; *(5a)*, 66810-76-2; *(5b)*, 66810-75-1; *(5c)*, 66810-74-0; *(5d)*, 13616-48-3; *(6a)*, 66810-73-9; *(6b)*, 66810-72-8; *(6c)*, 66810-71-7; *(6d)*, 66810-70-6

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[2] For a survey up to early 1976, see *H. P. Abicht, K. Issleib*, Z. Chem. *17*, 1 (1977).
[3] *D. Seebach, K. H. Geiss*, Angew. Chem. *86*, 202 (1974); Angew. Chem. Int. Ed. Engl. *13*, 202 (1974); *K. H. Geiss, D. Seebach, B. Seuring*, Chem. Ber. *110*, 1833 (1977).
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Table 1. Products of types *(3)*, *(4)*, and *(5)* obtained from benzyl alcohols and alkyl halides or carbonyl compounds. The yields of *(3a)*—*(3g)* and *(5a)*—*(5d)* are based on the electrophile. The air bath temperatures recorded on bulb-to-bulb distillation (Büchi GKR 50) are given as boiling points.

Reactants		Products	Yield [%]	M.p. [°C] or B.p. [°C/torr]
(2) +	Methyl iodide	*(3a)*, E = CH_3	30	115/20
(2) +	Butyl iodide	*(3b)*, E = *n*-C_4H_9	Trace	
(2) +	Butyl bromide	*(3b)*, E = *n*-C_4H_9	21	
(2) +	Butyl chloride	*(3b)*, E = *n*-C_4H_9	55	72/0.1
(2) +	Iodine	*(3c)*, E = I	58	91—93
(2) +	Cyclohexanone	*(3d)*, E = $C(OH)(CH_2)_5$	71	55—57
(2) +	4-*t*-Butyl-cyclohexanone	*(3e)*, E = $C(OH)(CH_2)_2CH(CH_2)_2$ with $C(CH_3)_3$	68	122—126
(2) +	Benzaldehyde	*(3f)*, E = $CH(OH)C_6H_5$	95	76
(2) +	Formaldehyde	*(3g)*, E = CH_2OH	70	63–65
(2) +	Carbon dioxide	*(4a)*, R/R′ = O	50	72—74
	(3d)	*(4b)*, R/R′ = $(CH_2)_5$	95	145/10
	(3e)	*(4c)*, R/R′ = $(CH_2)_2CH(CH_2)_2$ with $C(CH_3)_3$	92	70–75/3 × 10^{-2}
	(3f)	*(4d)*, R = C_6H_5, R′ = H	85	35
	(3g)	*(4e)*, R = R′ = H	88	192/760
(6a) +	Benzaldehyde	*(5a)*, R = H, R′ = CH_3	88	156—159
(6b) +	Benzaldehyde	*(5b)*, R = H, R′ = C_2H_5	82	131—135
(6c) +	Benzaldehyde	*(5c)*, R = H, R′ = C_4H_9	92	118—119
(6d) +	Benzaldehyde	*(5d)*, R = R′ = CH_3	86	oil

Other α-phenylalkanols react in the same way as benzyl alcohol. Thus we obtained the benzhydrols *(5a)*, *(5b)*, *(5c)* (mixture of diastereomers), and *(5d)* on treatment of the *ortho*-lithiated derivatives *(6a)*—*(6d)* (Table 1) of 1-phenylethanol, -1-propanol, -1-pentanol, and 2-phenyl-2-propanol, respectively, with benzaldehyde.

General procedure

A solution of *n*-butyllithium (20 mmol, *ca.* 1.5 M in hexane) is added in two portions, one half over a period of 10 min and the second all at once, to a vigorously stirred mixture of benzyl alcohol (10 mmol), light petroleum (b.p. 30—40 °C; 20 ml), and tetramethylethylenediamine (TMEDA) (20 mmol) at room temperature under an inert atmosphere. After heating under reflux for 11 h the mixture is cooled to −78 °C and the electrophile (7 mmol) is added. The temperature is allowed

Simple Method for the Esterification of Carboxylic Acids[1]

By *Bernhard Neises* and *Wolfgang Steglich*[*]

In spite of its successful use in the synthesis of some sugar and amino acid derivatives[3b] the dicyclohexylcarbodiimide (DCC)[2, 3a] method has not been generally adopted as a method for the preparation of carboxylates and thiolates,

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chiefly because of the variable yields, which are satisfactory only in the case of phenols and thiophenols[4], and the tendency for undesirable *N*-acylureas to be formed. The favorable catalytic action of pyridine in such reactions[3] suggested that the 10^4-fold more effective acylation catalyst 4-dimethylaminopyridine (DMAP) might prove to be a useful agent in our present studies on the esterification of carboxylic acids[1, 5].

Indeed, we have found that addition of 3—10 mol % DMAP accelerates the DCC-activated esterification of carboxylic acids with alcohols or thiols to such an extent that formation of side products is suppressed and even sterically demanding esters *(1)* are formed in good yields at room temperature (see Table 1).

$$RCO_2H + R'XH \xrightarrow[DMAP]{C_6H_{11}N{=}C{=}NC_6H_{11}} RCOXR'$$

(1), X = O, S

Table 1. Esters and thioesters *(1)*.

	Compound	Yield [%] [a]
(1a)	Methyl 1-phenylcyclohexane-1-carboxylate	87
(1b)	Methyl cinnamate	98
(1c)	Methyl 4-methoxybenzoate	61
(1d)	Methyl 2,6-dihydroxybenzoate	96.5
(1e)	Methyl 2,4,6-trimethylbenzoate	74
(1f)	Methyl 1,6-dihydroxy-8-methoxy-3-methyl-anthraquinone-2-carboxylate (methyl dermoluteinate)	55
(1g)	Di-*tert*-butyl malonate	85.5, 29.5 [b]
(1h)	*tert*-Butyl hydrocinnamate	68
(1i)	*tert*-Butyl pentaacetyl-D-gluconate	82.5
(1j)	*tert*-Butyl 2,5-cyclohexadiene-1-carboxylate	84, 34 [b]
(1k)	*tert*-Butyl cinnamate	68
(1l)	*tert*-Butyl benzoate	40
(1m)	*tert*-Butyl 2,6-dihydroxybenzoate	54
(1n)	*tert*-Butyl 3,5-dinitrobenzoate	84
(1o)	Di-*tert*-butyl *rac*-4,4',6,6'-tetrachloro-diphenate	91.5
(1p)	Glycerol tristearate	87.5
(1q)	*S*-Ethyl propanethioate	85
(1r)	*S*-Ethyl 16-hydroxyhexadecanethioate	92
(1s)	*S*-Ethyl 2,5-cyclohexadiene-1-carbothioate	90
(1t)	*S*-*tert*-Butyl cyclohexanecarbothioate	91

[a] The yields refer to pure products and are not optimized. All esters gave correct elemental analyses and spectroscopic data consistent with their constitution. B.p. [and m.p.] of the new compounds: *(1i)* oil; *(1j)* 80 °C/0.5 torr (Kugelrohr); *(1m)* 135/0.5 (KR); *(1o)* [82—84 °C]; *(1r)* [57]; *(1s)* 60/0.2 (KR).
[b] Without DMAP addition.

Thus, the sensitive 2,5-cyclohexadiene-1-carboxylic acid is transformed into the *tert*-butyl ester *(1j)* and into the *S*-ethylthioester *(1s)* quite smoothly, while the method generally recommended for its esterification, namely the boron trifluoride-etherate method, can be used only for the preparation of esters of primary and secondary alcohols[6]. The *tert*-butyl esters of 3,5-dinitrobenzoic acid *(1n)* and glycerol tristearate *(1p)* can also be prepared by this method, in contrast to the non-catalyzed reaction in which *N*-acylureas are formed[7]. 2,4,6-Trimethylbenzoic acid, which can be regarded as inert under normal esterification conditions, reacts with methanol/DCC/DMAP to give the methyl ester *(1e)* in 74 % yield.

Also thioesters *(1)*[8] can be conveniently prepared by the DMAP-catalyzed DCC method, and the yields are considerably higher than those obtained in the non-catalyzed reaction[9]. As example it is shown that synthesis of the thioester *(1r)* of 16-hydroxyhexadecanoic acid is possible without protection of the hydroxy groups. In contrast to some of the other methods, the DCC/DMAP method has the advantage that the free thiols can be used.

The possibility of synthesizing *tert*-butyl esters reaches a limit with more bulky, *i.e.* sterically hindered carboxylic acids. Thus, in the case of adamantanecarboxylic acid, 1-phenylcyclohexane-1-carboxylic acid and 2,4,6-trimethylbenzoic acid the symmetrical anhydrides were isolated instead of the *tert*-butyl esters. The unreactive 4-methoxybenzoic acid also gives only the anhydride, together with some *N*-acylurea, whose formation has been established only in this reaction so far. In the esterification of *Z*-amino acids with *tert*-butyl alcohol or 2-methyl-2-propanethiol under standard conditions some racemization was observed, but this can be largely avoided at lower temperatures and with shorter reaction times.

Procedure

To a stirred solution of 10 mmol carboxylic acid in 10 ml anhydrous CH_2Cl_2 (in the case of sparingly soluble acids, in DMF) is added 30—110 mg DMAP and 20—40 mmol alcohol or thiol (10 mmol with alcohols or thiols which are not easily removable without significant loss; 3.4 mmol with glycerol). DCC is added to the reaction mixture at 0 °C, which is then stirred for 5 min at 0 °C and 3 h at 20 °C. Precipitated urea is then filtered off and the filtrate evaporated down *in vacuo*. The residue is taken up in CH_2Cl_2 and, if necessary, filtered free of any further precipitated urea. The CH_2Cl_2 solution is washed twice with 0.5 N HCl and with saturated $NaHCO_3$ solution, and then dried over $MgSO_4$. The solvent is removed by evaporation and the ester isolated by distillation or recrystallization. Crystalline products can be obtained in pure form by filtration on a short silica gel column (eluent CH_2Cl_2 or $CHCl_3$.

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(1a), 17380-78-8; *(1b)*, 103-26-4; *(1c)*, 121-98-2; *(1d)*, 2150-45-0; *(1e)*, 2282-84-0; *(1f)*, 27152-37-0; *(1g)*, 541-16-2; *(1h)*, 16537-10-3; *(1i)*, 66921-97-9; *(1j)*, 61812-52-0; *(1k)*, 14990-09-1; *(1l)*, 774-65-2; *(1m)*, 66921-96-8; *(1n)*, 5342-97-2; *(1o)*, 66921-95-7; *(1p)*, 555-43-1; *(1q)*, 2432-42-0; *(1r)*, 66921-94-6; *(1s)*, 66921-93-5; *(1t)*, 54829-37-7; 1-phenylcyclohexane-1-carboxylic acid, 1135-67-7; cinnamic acid, 621-82-9; 4-methoxybenzoic acid, 100-09-4; 2,6-dihydroxybenzoic acid, 303-07-1; 2,4,6-trimethylbenzoic acid, 480-63-7; 1,6-dihydroxy-8-methoxy-3-methylanthraquinone-2-carboxylic acid, 26071-13-6; malonic acid, 141-82-2; hydrocinnamic acid, 501-52-0; pentaacetyl-D-gluconic acid, 17430-71-6; 2,5-cyclohexadiene-1-carboxylic acid, 4794-04-1; benzoic acid, 65-85-0; 3,5-dinitrobenzoic acid, 99-34-3; *rac*-4,4',6,6'-tetrachlorodiphenic acid, 53663-22-2; stearic acid, 57-11-4; propionic acid, 79-09-4; 16-hydroxyhexadecanoic acid, 506-13-8; cyclohexanecarboxylic acid, 98-89-5; methanol, 67-56-1; *tert*-butanol, 75-65-0; glycerol, 56-81-5; ethanethiol, 75-08-1; *tert*-butanethiol, 75-66-1

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Photochemical Reductive *trans*-Elimination from *trans*-Diazidotetracyanoplatinate(IV)[**]

By *Arnd Vogler, Alfred Kern*, and *Jürgen Hüttermann*[*]

Oxidative additions and reductive eliminations number among the most important reactions of transition metal complexes and are of special utility in the chemistry of organometallic compounds. Reductive *cis*-eliminations have also been observed as light-induced processes[1]. Thus, irradiation of $[IrClH_2(PPh_3)_3]$ leads to *cis*-elimination of H_2 and formation of $[IrCl(PPh_3)_3]$ in a single step; the elimination of H_2 is concerted, no hydrogen atoms are formed in the photoprocess[1b]. Photochemical reductive *trans*-eliminations have so far not been reported. We have now been able to demonstrate such a reaction with $[Pt^{IV}(CN)_4(N_3)_2]^{2-}$, which on irradiation is quantitatively converted into $[Pt^{II}(CN)_4]^{2-}$.

Of particular interest to us was whether this two-electron reduction of Pt^{IV} proceeded *via* a Pt^{III} intermediate, since it is generally assumed that both thermal[2a] as well as photochemical[2b] conversions of Pt^{IV} into Pt^{II} complexes involve two successive one-electron reductions. Should a Pt^{III} intermediate not be formed, then there are two mechanistic possibilities: While the cleavage of the two ligands in *cis*-elimination obviously does not involve formation of ligand radicals in the initial reaction step[1b] this could be possible on steric grounds in the case of *trans*-eliminations.

We conclude from our investigations that two N_3 radicals are formed in the initial step of photochemical reductive *trans*-elimination from *trans*-$[Pt(CN)_4(N_3)_2]^{2-}$ by simultaneous two-electron reduction without formation of a Pt^{III} intermediate:

$$[Pt^{IV}(CN)_4(N_3)_2]^{2-} \rightarrow [Pt^{II}(CN)_4]^{2-} + 2N_3^{\cdot}$$

Reaction of $K_2[Pt(CN)_4Br_2]$[3] with a large excess of KN_3 in water (reaction time 2 d) afforded the compound $K_2[Pt(CN)_4(N_3)_2]$, which was isolated in analytically pure form after recrystallization from acetone. The *trans* structure (D_{4h}) of the anion follows from the appearance of an IR band[3] (2181 cm^{-1}) in the region of the CN stretching vibrations. The electron absorption spectrum shows only one intense maximum ($\lambda = 302$ nm, $\varepsilon = 18300$) in the longwave region which is assigned to a $(N_3 \rightarrow Pt)$CT transition.

Irradiation of the CT band of the salt dissolved in water led to rapid evolution of nitrogen according to

$$[Pt(CN)_4(N_3)_2]^{2-} \rightarrow [Pt(CN)_4]^{2-} + 3N_2$$

The spectral changes observed during the photolysis (Fig. 1) show that no other products are formed, since the final spectrum was identical with that of $[Pt(CN)_4]^{2-}$[4] after prolonged irradiation; nor was any free azide detectable[5]. On complete absorption of light by the starting complex, the photochemical formation of $[Pt(CN)_4]^{2-}$ followed a zero order reaction. At excitation wavelengths of 300, 333, and 366 nm the quantum yield for the formation of $[Pt(CN)_4]^{2-}$ in water was $\Phi = 0.34 \pm 0.02$; in acetonitrile and ethanol it increased to $\Phi = 0.58$ and 0.61 ± 0.02, respectively. Unlike in aqueous solution, photolysis in ethanol leads also to formation of N_3^- as well as evolution of N_2.

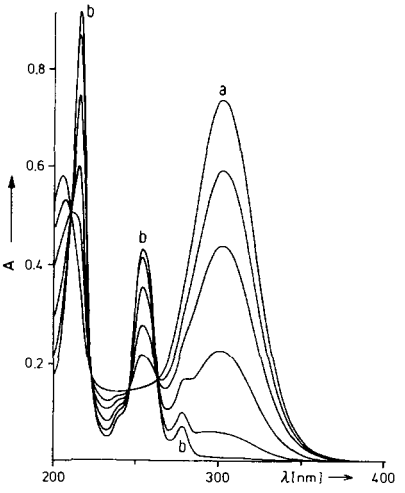


Fig. 1. Change in absorption spectrum during the photochemical transformation of *trans*-$[Pt(CN)_4(N_3)_2]^{2-}$, (a) in $Pt(CN)_4^{2-}$, (b) in aqueous solution (4×10^{-5} mol/l, 1 cm cuvette); excitation light: $\lambda = 300$ nm.

For identification of the primary products the photolysis of $[Pt(CN)_4(N_3)_2]^{2-}$ was carried out in ethanol glasses at 77 K and the irradiated samples investigated ESR spectroscopically. The observed signals could be assigned to N atoms[6] and CH_3CHOH radicals[7]. Pt^{III} signals[8] were not observed, even at 20 K.

N_3 radicals are extremely unstable. They dissociate very rapidly even at low temperatures into molecular nitrogen and N atoms[6b,c], which can be detected ESR spectroscopically. Finally, in the aqueous solution at room temperatures only N_2 is formed as stable end-product besides $[Pt(CN)_4]^{2-}$. In the presence of suitable reducing agents N_3 radicals can be reduced to azide[9]. The formation of CH_3CHOH radicals, which also were identified at low temperatures, and of free azide in the room temperature photolysis of $[Pt(CN)_4(N_3)_2]^{2-}$ in ethanol can be explained only in terms of a competing reaction of the N_3 radicals: besides dissociating, the N_3 radicals can obviously also be reduced by the solvent CH_3CH_2OH.

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CAS Registry numbers:
(1) (R = CH_3), 41308-25-2; *(1)* (R = C_6H_5), 41308-28-5; *(1)* (R = $CH(CH_3)_2$), 40854-38-4; *(1)* (R = $CH_2C_6H_5$), 66523-69-1; *(1)* (R = $CH(CH_3)C_6H_5$), 41308-29-6; *(2)* (R = CH_3), 66523-70-4; *(2)* (R = C_6H_5), 66523-71-5; *(2)* (R = $CH(CH_3)_2$, 66552-47-4; *(2)* (R = $CH_2C_6H_5$), 66523-72-6; *(2)* (R = $CH(CH_3)C_6H_5$), 66552-50-9; *(3)* (R = CH_3), 66523-76-0; *(3)* (R = C_6H_5), 66523-78-2; *(3)* (R = $CH(CH_3)_2$), 66523-80-6; *(3)* (R = $CH_2C_6H_5$), 66523-81-7; *(3)* (R = $CH(CH_3)C_6H_5$), 66523-83-9; $LiCH_3$, 917-54-4

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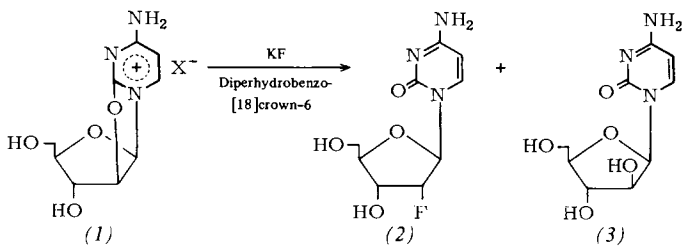
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A Simple Synthesis of 2′-Deoxy-2′-fluorocytidine by Nucleophilic Substitution of 2,2′-Anhydrocytidine with Potassium Fluoride/Crown Ether[1]

By *Rudolf Mengel* and *Wilhelm Guschlbauer*[*]

Fluorine-substituted natural products are interesting both from the biochemical and the pharmacological point of view[2]. Thus, fluorosugar-nucleosides show cytostatic and virostatic activities[3a]; poly-2′-deoxy-2′-fluorouridylic acid selectively inhibits viral polymerases[3b]. 2′-Deoxy-2′-fluoropyrimidine nucleosides have been shown to adopt the 3′-*endo* conformation[4a] and the corresponding polynucleotides behave like polyribonucleotides[4b].

In order to study the pharmacology of poly-2′-deoxy-2′-fluorocytidylic acid we have searched for a simple and productive method for the synthesis of 2′-deoxy-2′-fluorocytidine *(2)*. So far *(2)* has been obtained from 2′-deoxy-2′-fluorouridine *via* the 4-thio analog, methylation and ammonolysis[4a, 5] or, in small amounts, by heating the 2,2′-anhydrocytidine hydrofluoride *(1)*[6]. Experiments analogous to the synthesis of 2′-deoxy-2′-fluorouridine to transform *(1)* into *(2)* by heating with HF in dioxane have been unsuccessful[6]. We have found that the transformation *(1)* → *(2)* can be performed by anion activation of fluoride with crown ethers[7] under total exclusion of moisture. Besides the increased nucleophilicity of the crown ether activated F^-, its increased basicity is very notable[8] and traces of moisture will lead to hydrolysis of *(1)* with formation of 1-β-D-arabinofuranosylcytosine (aracytidine) *(3)*[6]. Thus reactions of *(1)* with KF/crown ether in acetonitrile, DMF, dioxane or HMPT yielded mainly *(3)*. Only after complete elimination of traces of water by azeotropic distillation with benzene from the mixture DMF/KF/crown ether could the desired nucleophilic fluorine substitution be achieved.



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

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Procedure:

A mixture of 100 ml dimethyl formamide, 1 ml diperhydrobenzo[18]crown-6, 2.5 g (43.1 mmol) KF (dried over P_2O_5, 100°C/0.01 torr) and 100 ml benzene is heated at 135°C in an oil bath and the benzene slowly distilled off. On completion of distillation, 1 g (3.32 mmol) 2,2′-anhydrocytidine hydrochloride[9] is added under a nitrogen atmosphere. After four hours' heating at 120°C, the solvent is removed in a rotatory evaporator, and the residual oil absorbed on 5 g silica gel and transferred to a silica gel column (2.3 × 35 cm, $CHCl_3$). Elution is started with 250 ml chloroform, followed by a chloroform/methanol mixture (3:2). The first 450 ml of eluate are discarded, the following 350 ml contains 380 mg *(2)* (yield 40 %). The product can be recrystallized from methanol or water, m.p. 163—167°C. Spectroscopic data (UV, NMR) are identical with those for an authentical sample[4a].

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CAS Registry numbers:
(1) (X = Cl), 10212-25-6; *(2)*, 10212-20-1; *(3)*, 147-94-4

[1] Nucleoside Transformations, Part 7. This work was performed in Saclay and supported by EURATOM through a short-term fellowship for *R. M.*—Part 6: *R. Mengel, U. Krahmer*, Carbohydr. Res., in press.
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High-Pressure Carbonylation of Metal-Coordinated Carbenes and Hydrogenolysis of the Ketene Complexes[1]

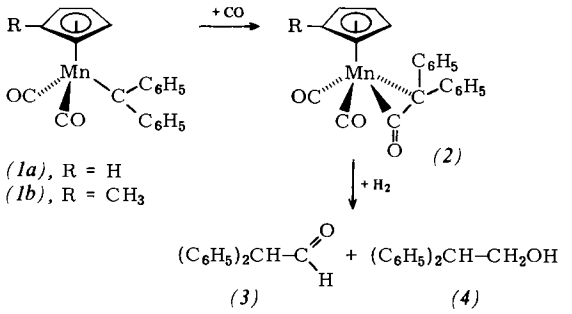
By *Wolfgang A. Herrmann* and *Johann Plank*[*]

The reactions of transition metal carbene complexes with carbon monoxide[2a] and hydrogen[2b] currently attract considerable attention in connection with reawakened interest in the Fischer-Tropsch synthesis[3]. While the two substrates have hitherto only been observed to displace the carbene ligand from the metal[2] we have now accomplished the first carbonylation of metal-coordinated carbenes to give the corresponding ketene complexes and their hydrogenolytic degradation to aldehydes and alcohols.

Under the conditions of high-pressure carbonylation the diphenylcarbenemanganese complexes *(1)*[4] (CO addition, 30—45 % conversion) give the diphenylketene complexes *(2)*. Their physical and spectroscopic data are in agreement with those of the compounds obtained by ligand displacement from the tetrahydrofuran complexes $(\eta^5\text{-}C_5H_4R)Mn(CO)_2THF$

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(R = H, CH_3) with diphenylketene[5]. Their identity was confirmed by X-ray structure analysis[5].



(1a), R = H
(1b), R = CH_3

(2) (3) (4)

This carbonylation reaction not only provides a new entry to the η^2-ketene complexes previously known only as isolated examples[6] but also constitutes preparative proof of the carbene→ketene conversion postulated by *Rüchardt* and *Schrauzer*[7] to occur in carbene-transition metal fragments. Moreover, our results substantiate the occurrence of free methoxy(phenyl)ketene deduced from the product spectrum of pressure carbonylation of pentacarbonyl(methoxyphenylcarbene)-chromium in the presence of vinylpyrrolidones[8].

The transformation of carbene complexes into ketene complexes is also of relevance as a model system for a step of the Fischer-Tropsch synthesis which probably proceeds *via* unstable metal-carbene intermediates[3] but is still largely unknown in its mechanistic details. We have now found that the carbonylation products *(2a)* and *(2b)* can be hydrogenolytically degraded under high pressure conditions to diphenylacetaldehyde *(3)* and 2,2-diphenylethanol *(4)* while *(1a)* and *(1b)* are not attacked by hydrogen below their decomposition temperatures. The carbonylation of carbenes can therefore successfully compete with reductive displacement of the carbene ligand from the metal. The reaction sequence carbene complex→ketene complex→aldehyde/alcohol provides a working hypothesis for the ultimate steps of the Fischer-Tropsch synthesis leading to "oxo products".

Procedure[9]

a) Carbene carbonylation: A solution of *(1a)* or *(1b)* (1 mmol) in tetrahydrofuran (30 ml) is treated in a 100-ml rotating autoclave with a glass insert with CO (650 bar initial pressure) at 50±5 or 35±5°C (jacket temperature) for 25 h. The brownish-yellow crude product obtained on evaporation with a water-aspirator is worked up by column chromatography on SiO_2 (activity II—III; 60×1.2 cm; +15°C), elution with benzene giving first a small amount of (η^5-C_5H_4R)$Mn(CO)_3$ as a fast-moving light yellow band which is followed by the bright yellow band of the ketene complex *(2a)* or *(2b)*. After recrystallization, the yellow compounds which are air-stable in the solid state are analytically pure (IR, MS, elemental analysis). Yield: *(2a)*, 122—167 mg (32—45%); *(2b)*, 116—161 mg (30—42%).

b) Ketene hydrogenation: *(2a)* or *(2b)* (2 mmol) is dissolved in tetrahydrofuran (30 ml) and reacted with H_2 (100-ml rotating autoclave with a glass insert, 20 h, 50±5°C jacket temperature, 750 bar initial pressure of H_2). High-vacuum distillation of the concentrated solution in a Kugelrohr apparatus (air-bath temperature 130—140°C) gives *ca.* 200 mg (51%) of a mixture of *(3)* (≈25%) and *(4)* (≈75%) as a yellowish oil (characterization by IR, MS, and ^{1}H-NMR).

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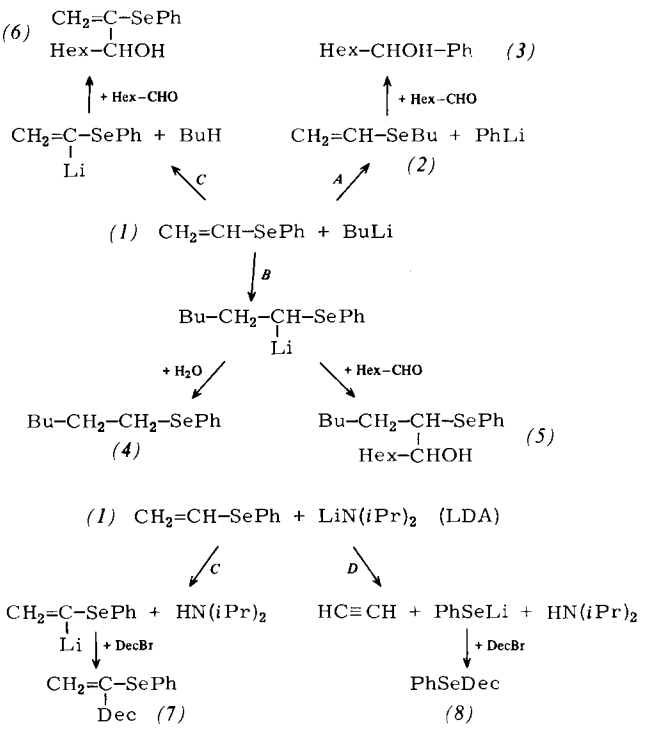
CAS Registry numbers:
(1a), 55971-21-6; *(1b)*, 55971-28-3; *(2a)*, 53265-44-4; *(2b)*, 53265-43-3; *(3)*, 947-91-1; *(4)*, 1883-32-5; CO, 630-08-0

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[6] The reaction of 9-diazoanthrone(10) with (η^5-C_5H_4R)$Mn(CO)_2$THF (R = H, CH_3) proceeds at normal pressure in the presence of CO to form the corresponding ketene complexes (yield 31—40%); the highly thermally stable carbene complexes which are usually formed cannot be isolated: *W. A. Herrmann, J. Plank*, unpublished experiments 1977/78.
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Reactivity of Phenyl Vinyl Selenide with Nucleophiles and Bases

By *Mireille Sevrin, Jean N. Denis*, and *Alain Krief*[*]

In continuation of our work on the reactivity of selenides with *n*-butyllithium[1] we have investigated the reaction of vinyl phenyl selenide *(1)* with various nucleophiles and bases



Scheme 1. Four possible modes of reaction of phenyl vinyl selenide *(1)* with nucleophiles. Route A: Se—C cleavage; route B: addition (in analogy to vinyl sulfides and silanes); route C: metalation (in analogy to vinyl sulfides and halides and ethyl vinyl ether); route D: elimination (in analogy to ethyl vinyl ether). Bu = *n*-butyl, Dec = *n*-decyl, Hex = *n*-hexyl, Ph = phenyl, *i*Pr = isopropyl.

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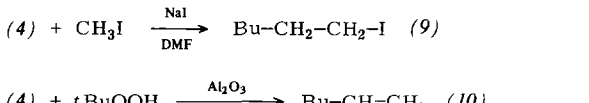
and have found that, depending upon the nature of the reagents and conditions used (solvent, temperature), all the possible reaction routes A, B, C and/or D outlined in Scheme 1 can be observed. Some of these reactions are of synthetic value.

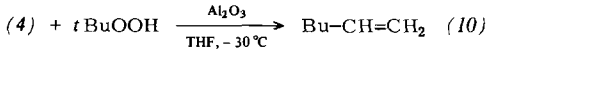
When phenyl vinyl selenide *(1)* is allowed to react with *n*-butyllithium in tetrahydrofuran (THF) for 1 h at −78 °C, and heptanal is then added, butyl vinyl selenide *(2)* (70%) and 1-phenyl-1-heptanol *(3)* (68%)[2] are formed *via* route A. Small amounts of hexyl phenyl selenide *(4)* (5%) and 2-phenylseleno-1-nonen-3-ol *(6)* (17%) are also formed, *via* addition (route B) and metalation (route C), respectively. When the reaction is performed at −30 to 0 °C the yield of addition product *(4)* increases (−10 °C: 28%) and that of the cleavage product decreases (−10 °C: 18%).

When THF is replaced by diethyl ether, route B largely predominates; if the reaction is conducted at 20 °C for 5 min before quenching with water, *(4)* is obtained in 65% yield[3]. With longer reaction times the yield of *(4)* drops considerably (30 min: 30%). The accompanying side-products were not identified[4, 5]. On addition of heptanal after 5 minutes reaction time at 20 °C, 40% of the corresponding 6-phenylseleno-7-tridecanol *(5)* is formed along with 10% of *(4)* (route B). *(2)* (13%) and *(3)* (20%) (*via* route A) as well as *(6)* (20%) (*via* route C) are also obtained.

Lithium diisopropylamide (LDA) is found to be the most effective reagent for metalation of the title compound: no C—Se cleavage was observed with this reagent[6]. However, depending on the nature of the solvent, elimination (route D) can occur as well as metalation (route C). For example, reaction of *(1)* and 1.5 equivalents LDA at −78 °C for one hour furnishes a carbanion, which can be trapped with D_2O in 80% yield as 1-deuteriovinyl phenyl selenide and with heptanal in 40% yield as 2-phenylseleno-1-nonen-3-ol *(6)*.

In hexamethylphosphoric triamide (HMPT)/THF (1:20, −78 °C, 1 h)[7] the alkylation is even more strongly favored. Addition of one equivalent of decyl bromide (−78 °C, 2 h) leads to 2-phenylseleno-1-dodecene *(7)* (70%) (route C) and decyl phenyl selenide *(8)* (23%) (route D). In HMPT/THF (1:3) the elimination reaction predominates; the selenide *(8)* is formed in 65% yield.





We have used the hexyl phenyl selenide *(4)* obtained *via* route B for the synthesis of hexyl iodide *(9)* and 1-hexene *(10)* (80% and 74% yield, resp.)[8]. 2-Phenylseleno-1-dodecene *(7)* can be readily hydrolyzed to 2-dodecanone (91% yield)[9].

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CAS Registry numbers:
(1), 35167-28-3; *(2)*, 66769-95-7; *(3)*, 614-54-0; *(4)*, 63866-88-6; *(5)*, 66769-94-6; *(6)*, 66769-93-5; *(7)*, 66769-92-4; *(8)*, 61539-89-7; *(9)*, 638-45-9; *(10)*, 592-41-6

[1] *W. Dumont, P. Bayet, A. Krief*, Angew. Chem. *86*, 857 (1974); Angew. Chem. Int. Ed. Engl. *13*, 804 (1974); *D. Seebach, A. K. Beck, ibid. 86*, 859 (1974) bzw. *13*, 806 (1974).

[2] To a solution of *(1)* (1 mmol) in THF (2 ml) is added *n*-butyllithium (1 mmol) at −78 °C under argon and the mixture stirred for one hour. After slow addition of 1 mmol heptanal in THF (2 ml) the solution is allowed to stand for 2 h at −78 °C and 1 h at 25 °C, hydrolyzed, and worked up in the usual way.

[3] A solution of *(1)* (1 mmol) in ether (2 ml) is treated at 20 °C under argon with 1 mmol *n*-butyllithium and the mixture stirred for 1 h. After hydrolysis the mixture is extracted with ether and the extract dried. Distillation of the crude product affords pure *(4)*, b.p. 70 °C/0.1 torr, identical with an authentic sample.

[4] During the completion of our work a short communication appeared, dealing in part with the reaction of *(1)* with *n*-butyllithium: *Th. Kauffmann, H. Ahlers, H. J. Tilhard, A. Woltermann*, Angew. Chem. *89*, 760 (1977); Angew. Chem. Int. Ed. Engl. *16*, 710 (1977).

[5] If the reaction mixture is stirred for a longer time the initially formed α-selenocarbanion rearranges; as in the case of the analogous sulfur compounds, ring-metalated derivatives are formed. With CH_3I, a mixture of hexyl tolyl selenides is obtained; with heptanol, no β-selenoalcohol *(5)* is formed, but instead a mixture of 1-tolyl-1-hexanols is obtained.

[6] a) Synthesis of 1-lithio-1-methylseleno-1-octene (75%) from 1,1-bis(methylseleno)-1-octene by C—Se cleavage: *A. Krief*, lecture at Rouen (France), July 3, 1977; b) Synthesis of β-lithio-β-phenylselenostyrene by C—Se cleavage: *B. T. Gröbel, D. Seebach*, Chem. Ber. *110*, 867 (1977).

[7] A solution of LDA (3 mmol) in THF (3 ml) is treated with 2 mmol *(1)* in HMPT/THF (1:9) at −78 °C and the mixture stirred for 1 h. After addition of 2 mmol decyl bromide in THF (3 ml) the reaction mixture is stirred for 2 h, hydrolyzed, extracted with ether, and the extract dried. The crude product is purified by preparative thick layer chromatography (SiO_2, (Merck) 2 mm, pentane, $R_f = 0.62$).

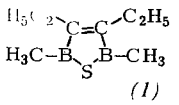
[8] *M. Sevrin, W. Dumont, L. Hevesi, A. Krief*, Tetrahedron Lett. *1976*, 2647; *D. Labar, W. Dumont, L. Hevesi, A. Krief, ibid.*, in press.

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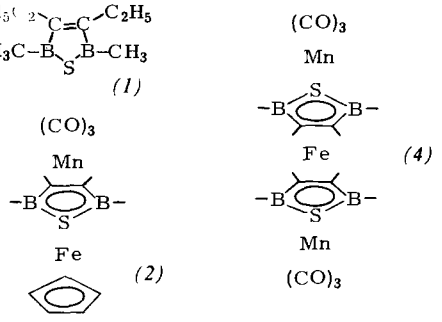
Synthesis and Structure of the Tetradecker Complex Bis(tricarbonylmanganese-μ,η-thiadiborolene)iron[1]

By *Walter Siebert, Christian Böhle, Carl Krüger*, and *Yi-Hung Tsay*[*]

The possibility of constructing oligo-decker and poly-decker complexes (quadruple-decker[2a], multiple-decked stacked compounds[2b]) has already received consideration. We have extended our studies on Lewis acid ligands in sandwich and triple-decker complexes[3] to tetradecker complexes and now wish to report the first trinuclear complex *(4)* containing two bridging thiadiborolene and six terminal carbon monoxide ligands.



(1)



(4)

(2)

Simultaneous reaction of the thiadiborolene derivative *(1)*[4a] with $Mn_2(CO)_{10}$ and $[(C_5H_5)Fe(CO)_2]_2$ gives the green air-stable triple-decker complex *(2)*, m.p. 194 °C [^{1}H-NMR: $\delta = 3.85$ (s, 5), 3.0—2.1 (m, 4), 1.53 (s, 6), 1.36 (t, 6) in CS_2 rel. to TMS int.; ^{11}B-NMR: $\delta = 18.0$ in CS_2 rel. to $Et_2O \cdot BF_3$ ext.; IR: $\nu(CO) = 2031$ (s), 1946 (s), 1935 (s) cm^{-1} in C_2Cl_4; MS: M^+ (14), $\{M-3CO\}^+$ (100), $\{(C_5H_5)FeL\}^+$ (9), ...]. A first example of this triple-decker type of complex containing *different* terminal ligands, *viz.* $[(C_5H_5)Co(C_2B_3)Fe(CO)_3]$, has recently been described[5].

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As in ferrocene, the C_5H_5 ligand of *(2)* can be replaced with $C_6H_6/AlCl_3$ to give the red-violet triple-decker salt *(3)* which is sensitive to hydrolysis. Its thermolysis at 140°C/0.1 torr affords a low yield of the orange-red tetradecker complex *(4)*, m.p.: dark coloration above 155°C, decomposition at 210°C:

$$2\ [(C_6H_6)Fe\cdot\textit{(1)}\cdot Mn(CO)_3]^{\oplus}AlCl_4^{\ominus} \xrightarrow{\Delta} \underset{(3)}{} \textit{(4)} + 2\ C_6H_6 + [FeCl_2,\ 2\ AlCl_3]$$

The IR spectrum of *(4)* contains three strong bands at 2033, 1955, and 1944 cm^{-1} (in C_2Cl_4) showing a significant shift relative to the CO stretching vibrations of the triple-decker $[(CO)_3Mn\cdot\textit{(1)}\cdot Mn(CO)_3]$ (2021, 1966, 1956 cm^{-1}, in C_2Cl_4)[4b]. The FD mass spectrum exhibits an isotopic pattern for the molecular ion $[(CO)_3MnL]_2Fe^+$ [L = *(1)*] ($I_{rel}=100$ based on $^{11}B_4$) which is due to the presence of four boron atoms. Apart from M^+ (12), the following principal fragments are observed at 70 eV: $\{M-3CO\}^+$ (50), $\{Mn_2L_2Fe\}^+$ (16), $\{MnLFe-28\}^+$ (8), MnL^+ (4), L^+ (12), $(C_2H_5)_2C_2BCH_3^+$ (100).

The structure of the complex *(4)* is confirmed by X-ray structure analysis[6]. Both of the independent molecules in the triclinic unit cell have a center of inversion (Fe); they differ in the conformation of the substituents on the planar ($\pm 0.01\times10^{-10}$ m) C_2B_2S rings. Owing to the center of inversion these rings have a mutual transoid arrangement whereas they are staggered (each rotated 90°) in the comparable triple-decker sandwich $(C_2B_2S)_3Co_2$[7]. The bond lengths of the bifacially coordinated ring atoms are lengthened in a typical manner relative to the corresponding distances in unifacially coordinated C_2B_2S rings[8] (average values: B—S 1.928(7), B—C 1.544(9), C—C (1.477(9)). The Fe—Mn distances are 3.408(1) and 3.391(1) 10^{-10} m.

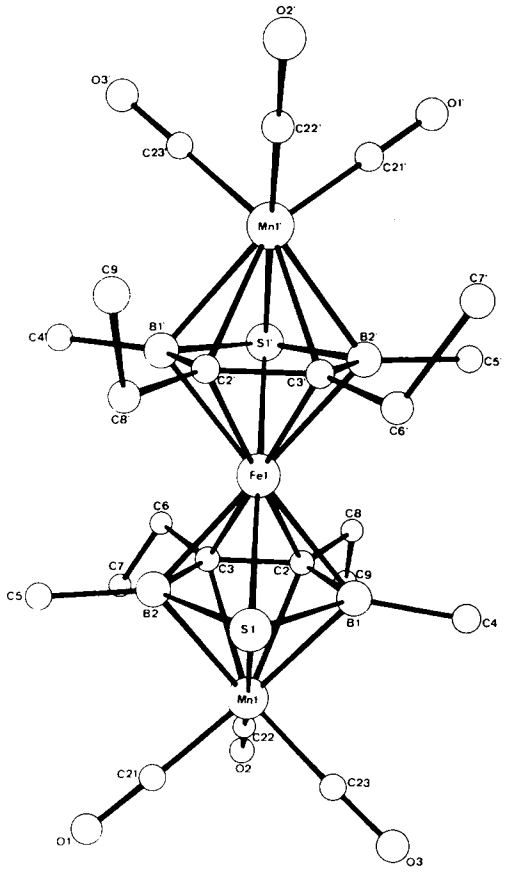


Fig. 1. Molecular structure of complex *(4)* in the crystalline state.

We attribute this first example of *trans* orientation of neighboring C_2B_2S rings to formation of two π^6-electron systems in the central $(C_2B_2S)_2Fe$ sandwich. Two equivalent approaches can be adopted in describing the bonding in *(4)*. According to the π^6/d^{6-8} viewpoint[9a] *(4)* is the first member of the tetradecker family with 42—48 valence electrons; four planes of ligands (two C_2B_2S rings as π^6-electron donors and two $(CO)_3$ groups as σ^6-electron donors) are held together by three d^6 metal ions. According to the *closo* approach[9b], *(4)* can be regarded as a double cluster of two pentagonal bipyramids with a common Fe apex; $2n+2=16$ skeletal electrons are necessary to hold the C_2B_2SMnFe clusters together; they are provided by C(2 × 3), B(2 × 2), S(4), Mn(1), and Fe(1).

Procedure

A mixture of *(1)* (0.85 g, 5.12 mmol), $Mn_2(CO)_{10}$ (1.49 g, 3.84 mmol) and $[C_5H_5Fe(CO)_2]_2$ (1.35 g, 3.84 mmol) in 20 ml mesitylene is heated under nitrogen for 0.5 h at 165°C. After removal of solvent the residue is taken up in hexane and chromatographed on dry silica gel (Woelm 100–200). The first band contains $Mn_2(CO)_{10}$ and some $[(CO)_3Mn\cdot\textit{(1)}\cdot Mn(CO)_3]$, the second band green *(2)* (0.82 g; best yield in analogous reactions 37 %).

A mixture of *(2)* (0.25 g, 0.58 mmol) and $AlCl_3$ (0.25 g, 1.87 mmol) in benzene (20 ml) is stirred under nitrogen for 0.5 h at 90°C. Reddish-violet *(3)* precipitates out. On heating *(3)* (0.2 g, 0.33 mol) to 140—160°C/0.1 torr a yellow-brown sublimate is obtained, which on recrystallization from CS_2 affords orange-red crystals; yield 3 mg (2.7 %).

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CAS Registry numbers:
(1), 54677-51-9; *(2)*, 66921-71-9; *(3)*, 66984-57-4; *(4)*, 66921-70-8; $Mn_2(CO)_{10}$, 10170-69-1; $[(C_5H_5)Fe(CO)_2]_2$, 12154-95-9

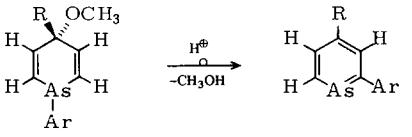
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[4] a) *W. Siebert, R. Full, J. Edwin, K. Kinberger*, Chem. Ber. *111*, 823 (1978); b) *W. Siebert, K. Kinberger*, Angew. Chem. *88*, 451 (1976); Angew. Chem. Int. Ed. Engl. *15*, 434 (1976).
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[6] Crystal data: $a=9.679(2)$, $b=12.286(2)$, $c=13.364(3)$ (all values in 10^{-10} m), $\alpha=113.38(2)$, $\beta=97.61(2)$, $\gamma=80.08(1)°$, space group $P\bar{1}$, $Z=2$, $d_{ber}=1.539\ g\cdot cm^{-3}$; 4986 reflections, 1150 unobserved; $R=0.046$.
[7] *C. Krüger, J. C. Sekutowski*, unpublished.
[8] *W. Siebert, T. Renk, K. Kinberger, M. Bochmann, C. Krüger*, Angew. Chem. *88*, 850 (1976); Angew. Chem. Int. Ed. Engl. *15*, 779 (1976); *W. Siebert, R. Full, J. Edwin, K. Kinberger, C. Krüger*, J. Organomet. Chem. *131*, 1 (1977).
[9] a) *J. W. Lauher, M. Elian, R. H. Summerville, R. Hoffmann*, J. Am. Chem. Soc. *98*, 3219 (1976); b) *K. Wade*, Adv. Inorg. Chem. Radiochem. *18*, 1 (1976).

4-Alkoxy-1-phenylphosphacyclohexadiene → 1-Alkoxy-1-phenyl-λ⁵-phosphorin Rearrangement

By *Gottfried Märkl, Rainer Liebl*, and *Alois Hüttner*[*]

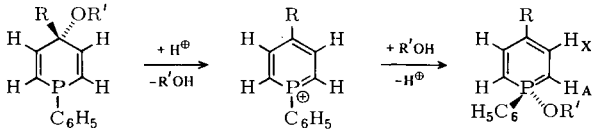
4-Alkyl- or 4-aryl substituted 1-aryl-4-methoxy-1-arsa-2,5-cyclohexadienes *(1)* undergo H^+-catalyzed rearrangement to 2-aryl-λ³-arsenins *(2)*[1].

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(1) (2)

The 4-alkyl- or 4-aryl-substituted 4-alkoxy-1-aryl-1-phospha-2,5-cyclohexadienes *(3)*[2], which are readily accessible by analogy to *(1)*, behave in a completely different manner. In the presence of catalytic amounts of *p*-toluenesulfonic acid in benzene (25 °C, 12 h) they give good yields of the corresponding 1-alkoxy-1-phenyl-λ^5-phosphorins *(4)*, the first *C*-monosubstituted λ^5-phosphorins (Table 1).



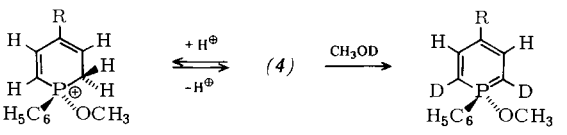
(3) (5) (4)

intramolecular rearrangement; the products of intermolecular rearrangement are formed in relative yields of below 10%.

3) If the rearrangement *(3)* → *(4)* is carried out in alcohols HOR″ instead of benzene, then HOR″ competes for *(5)* only to a limited extent with the alcohol HOR′ liberated by ether cleavage. Rearrangement of *(3c)* (R′ = CH_3) in ethanol, isopropyl alcohol, and *tert*-butyl alcohol gives the λ^5-phosphorins of the competing reaction in yields of 80, 40, and 15%, respectively. Thioalcohols and phenols cannot compete for *(5)*.

The pronounced upfield shift of the ring protons H^2, H^6 in *(4)* (see Table 1) support the assumption[7] that the λ^5-phosphorins *(4)* exist as cyclically conjugated alkylidenephosphoranes with a high π-electron density in positions 2, 4, and 6 due to ylidic resonance.

The λ^5-phosphorins *(4)* are protonated exclusively at C-2 by mineral acids to form *(6)*[8].



(6) (4) (7)

Table 1. Physical data of the 4-substituted 1-alkoxy-1-phenyl-λ^5-phosphorins *(4)*.

	R R′	Yield [%]	M.p. [°C] [a]	^{1}H-NMR ($CDCl_3$) [b] δ	MS (70 eV) (rel. int. [%])	UV (EtOH) λ_{max} [nm] (ε)
(4a)	*c*-C_6H_{11} CH_3	75	71	OCH_3: 3.05 (d), J_{PH} = 13 Hz; H_A: 4.79 (2d), $J_{H_AH_X}$ = 11.2, J_{PH_A} = 9.5 Hz; H_X: 7.31 (2d), J_{PH_X} = 34 Hz	M^+, 286 (71); $[M-C_3H_7]^+$, 243 (100); $[C_6H_5{-}P{-}OCH_3]^+$, 139 (52); $[C_6H_5PH]^+$, 109 (36)	358 (4600) 329 (3900)
(4b)	$(CH_3)_3C$ CH_3	55	58	OCH_3: 3.10 (d), J_{PH} = 13 Hz; H_A: 4.73 (2d), $J_{H_AH_X}$ = 11.0, J_{PH_A} = 9.5 Hz; H_X: 7.48 (2d), J_{PH_X} = 34 Hz	M^+, 260 (21); $[M-CH_3]^+$, 245 (100); $[C_6H_5{-}P{-}OCH_3]^+$, 139 (11); $[C_6H_5PH]^+$, 109 (16)	350 (4900) 325 (4100)
(4c)	C_6H_5 CH_3	65	73	OCH_3: 3.18 (d), J_{PH} = 13 Hz; H_A: 4.96 (2d), $J_{H_AH_X}$ = 11.5, J_{PH_A} = 9.18 Hz; H_X: 7.79 (2d), J_{PH_X} = 36 Hz	M^+, 280 (71); $[M-CH_2O]^+$, 250 (14); $[M-OCH_3]^+$, 249 (14); $[C_6H_5{-}P{-}OCH_3]^+$, 139 (100)	352 (sh) (6000) 303 (20400)
(4d)	*c*-C_6H_{11} C_2H_5	80	30	CH_3: 1.16 (t), J_{HH} = 7 Hz; OCH_2: 3.36 (2q), J_{PH} = 10.0 Hz; H_A: 4.81 (2d), $J_{H_AH_X}$ = 12.0, J_{PH_A} = 9.5 Hz; H_X: 7.48 (2d), J_{PH_X} = 34 Hz	M^+, 300 (100); $[M-C_3H_7]^+$, 257 (68); $[257-C_2H_4]^+$, 229 (26)	358 (4100) 327 (3500)
(4e)	$(CH_3)_3C$ C_2H_5	78	oil	$(CH_3)_3C$: 1.23 (s); CH_2CH_3: 1.10 (t), J_{HH} = 7 Hz; OCH_2: 3.37 (2q), J_{PH} = 10 Hz; H_A: 4.81 (2d), $J_{H_AH_X}$ = 12.0, J_{PH_A} = 9.6 Hz; H_X: 7.47 (2d), J_{PH_X} = 35 Hz		358 (4000) 335 (3400) (in $CHCl_3$)

[a] Recrystallization from light petroleum (50—70 °C). [b] 60 MHz, 100 MHz spectra, ^{31}P-broad band decoupling. The ring protons H_A, H_X appear as AA′XX′Y systems; H_A and H_X show characteristic fine structure. The values given for $J_{H_AH_X}$ are approximate values.

The ^{31}P-NMR chemical shifts ($CDCl_3$, H_3PO_4 ext., PH broad-band decoupling) of *(4a)*, *(4b)* and *(4c)* (δ = −40.4, −40.2 and −38.3, respectively) are in complete agreement with those of 1,1-dimethoxy- and 1-diethylamino-1-ethoxy-2,4,6-triphenyl-λ^5-phosphorin (δ = −65.2 and −45.0, respectively)[9].

The differing behavior of *(1)* and *(3)* is rationalized in terms of the greater energy of the P—C bond (65 kcal/mol)[3] compared with that of the As—C bond (≈ 50—55 kcal/mol)[4]; the greater stability of the λ^5-phosphorins relative to λ^5-arsenins also plays a role.

The following results suggest that the rearrangement *(3)* → *(4)* is predominantly intramolecular, proceeding *via* the planar[5] phosphorinium ions *(5)* (phosphorinium ions have already been proposed as intermediates in the formation of λ^5-phosphorins from triarylpyrylium salts and phenylphosphane[6]):

1) The mixtures of *cis-(3)* and *trans-(3)* obtained in the synthesis rearrange to *(4)* at the same rate as the pure isomers.

2) A crossover experiment with *(3a)* and *(3e)* gives almost exclusively the λ^5-phosphorins *(4a)* and *(4e)* resulting from

The nucleophilic character of positions 2 and 6 of *(4)* is apparent from the rapid uncatalyzed H/D exchange of H^2, H^6 in CH_3OD at room temperature; *(7a)*, R = *c*-C_6H_{11}, m.p. 71—72 °C; *(7c)*, R = C_6H_5, m.p. 74—75 °C.

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cis-(3a), 65683-77-4; *trans-(3a)*, 65683-78-5; *cis-(3b)*, 65683-79-6; *trans-(3b)*, 65683-80-9; *cis-(3c)*, 65683-76-3; *trans-(3c)*, 65683-75-2; *cis-(3d)*, 66809-07-2; *trans-(3d)*, 66809-08-3; *cis-(3e)*, 66809-09-4; *trans-(3e)*, 66809-10-7; *(4a)*, 66809-11-8; *(4b)*, 66809-12-9; *(4c)*, 66809-13-0; *(4d)*, 66809-14-1; *(4e)*, 66809-15-2; *(6c)*, 66809-16-3; *(7a)*, 66809-17-4; *(7c)*, 66809-18-5

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[8] ^{1}H-NMR ($CDCl_3/CF_3COOH$) *(6c)*, $R=C_6H_5$; OCH_3: 3.77 (d), $J_{PH}=13$ Hz; CH_2: ABX spectrum, AB parts at 3.36 and 3.43, $J_{AB}=11$, $|J_{AX}+J_{BX}|\approx 10$ Hz.
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Synthesis of *N*-Methyliminosulfur Tetrafluoride, $CH_3N{=}SF_4$, from the Cation $CH_3NSF_3^+$[**]

By *Rüdiger Mews*[*]

The addition of polar reagents RF to the formal triple bond of NSF_3 to give products of the type $R_2N{-}SF_5$ (*e.g.* R = H, Cl[1]) has been suggested to proceed *via* the following mechanism[2]:

$$N{\equiv}SF_3 + \overset{\delta+}{R}{-}\overset{\delta-}{F} \longrightarrow \{R{-}N{=}SF_3^+F^-\} \longrightarrow \{RN{=}SF_4\}$$
(1) *(2)* *(3)*

$$\xrightarrow{RF} \{RN{-}SF_5^-R^+\} \longrightarrow R_2N{-}SF_5$$
(4) *(5)*

The intermediates *(2)*, *(3)* and *(4)*, however, could previously never be isolated, since the cation in *(2)* is attacked by the nucleophilic F^-, and the pentacoordinated sulfur in *(3)* reacts, with increase in coordination number, to give the anion *(4)*, from which the compound *(5)* is then formed. We have now been able to carry out the first stepwise addition of "methyl fluoride" and to isolate the intermediates of type *(2)* and *(3)*.

$$(1) + CH_3Br + AgAsF_6 \xrightarrow[-AgBr]{SO_2} CH_3OSO^+AsF_6^- + (1)$$

$$(1) \xrightarrow{-SO_2} CH_3NSF_3^+AsF_6^-$$
(6)

As methylating reagent we used the cation CH_3OSO^+[3], also readily accessible *via* other routes. This reaction is generally applicable to alkyl halides RX (*e.g.* $R=CH_3$, C_2H_5; X = Br, I); the alkylation step can be regarded as nucleophilic exchange of SO_2 by the weak base *(1)*. $ROSO^+$ is an extremely good alkylating agent, enabling even the preparation of the cations $R_fRNSF_2^+$ and R_fRNSO^+ ($R_f=CF_3$, C_2F_5, *i*-C_3F_7; $R=CH_3$, C_2H_5) from the corresponding perfluorinated alkyliminosulfur difluorides and oxides[4].

In the ^{19}F- and ^{1}H-NMR spectra the colorless salt *(6)*, m.p. 190 °C, shows the expected quartet ($\delta_{SF}=48.2$; $\delta_{CH}=3.87$; $J_{HF}=8.7$ Hz; $\delta_{AsF}=-60.85$; $J_{AsF}\approx 900$ Hz). We assign the band observed at 1790 cm^{-1} in the IR spectrum to the SN stretching vibration; it thus lies about 100 wavenumbers higher than the previously reported highest ν_{SN} band of $F_3B{\cdot}NSF_3$[5]. On heating *(6)* with an excess of NaF *in vacuo* at 160 °C the covalent tetrafluoro derivative *(7)* is formed in 67 % yield.

$$(6) + NaF \xrightarrow{\Delta} CH_3N{=}SF_4 + NaAsF_6$$
(7)

Compound *(7)* is a colorless stable liquid, b.p. 21.8 °C/760 torr (extrapolated). At room temperature the ^{19}F-NMR spectrum shows a broad signal ($\delta_{SF}=71.3$), the ^{1}H-NMR spectrum the expected quintet ($\delta_{CH}=2.97$, $J_{HF}=3.65$ Hz)[6]. In the IR spectrum ν_{SN} appears at 1313/1307 cm^{-1}, the SF stretching vibrations lie in the region between 800 and 900 cm^{-1} (852, 815 cm^{-1}) characteristic for S^{VI} derivatives. The reaction behavior of *(7)* ought to resemble that of $O{=}SF_4$. As expected *(7)* is a weaker acceptor for F^-; a salt analogous to $Cs^+OSF_5^-$[7] is not stable at room temperature.

$$CsF + (7) \not\longrightarrow Cs^+CH_3NSF_5^-$$

$$BF_3 + (7) \longrightarrow CH_3NSF_3^+BF_4^-$$
(8)

Conversely the ability of *(7)* to act as donor of F^- is increased. Thus, the tetrafluoroborate *(8)* is extraordinarily stable and sublimes *in vacuo* only above room temperature.

Procedure

a) $CH_3NSF_3^+AsF_6^-$ *(6)*: A mixture of $AgAsF_6$ (8.50 g, 28.6 mmol), *(1)* (3.50 g, 34 mmol) and CH_3Br (3.10 g, 32.6 mmol) in 10 ml SO_2 is stirred for 20 h at room temperature. After filtration and removal of solvent by evaporation 8.35 g of crystalline crude product is obtained (yield 95 %). Reaction of *(7)* with AsF_5 in SO_2 affords analytically pure *(6)*.

b) CH_3NSF_4 *(7)*: *(6)* (8.06 g, 26.25 mmol) is heated with an excess of NaF for 20 h at 160 °C *in vacuo* and the volatile products are collected in a trap cooled with liquid N_2. Repeated fractional condensation (−80 °C, −110 °C, liquid air) at −110 °C affords 2.40 g *(7)* (yield 67 %).

c) $CH_3NSF_3^+BF^-$ *(8)*: A mixture of *(7)* (0.94 g, 6.9 mmol) and BF_3 (0.61 g, 9.0 mmol) is condensed with 5 ml SO_2 in a glass bomb and brought to room temperature. After removal of SO_2 the residue is dried by suction: 1.40 g colorless *(8)*, m.p. 116 °C (yield quantitative). NMR: $\delta_{SF}=47.90$, $\delta_{BF_4}=-145.7$; $\delta_{CH}=3.73$; $J_{HF}=8.6$ Hz.

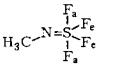
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CAS Registry numbers:
(1), 15930-75-3; *(6)*, 66901-77-7; *(7)*, 66901-49-3; *(8)*, 66901-48-2; CH_3Br, 74-83-9; NaF, 7681-49-4; BF_3, 7637-07-2

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[**] This work was supported financially by the Niedersächsisches Zahlenlotto.

[1] *A. F. Clifford, L. C. Duncan*, Inorg. Chem. *5*, 692 (1966); *A. F. Clifford, G. R. Zeilenga, ibid. 8*, 979 (1969).
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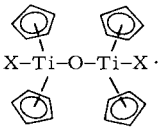


is already slowed down at room temperature (the halfwidth of of the ^{19}F-signal is 200 Hz). Below 0 °C both the ^{19}F- as well as the ^{1}H-signal changes into a complex multiplet the peaks of which continually change, down to the lowest temperature of measurement. The complexity of the spectra is caused, on the one hand, by exchange processes at the sulfur atom and, on the other, by hindrance of inversion at the nitrogen (rotation about the C—N axis) [cf. also, discussion of the spectrum of CF_3NSF_4: *E. L. Muetterties, W. Mahler, K. J. Packer, R. Schmutzler*, Inorg. Chem. *3*, 1298 (1964)].
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An Organometallic Complex with Coordinatively Bound Water: $[\{(\eta\text{-}C_5H_5)_2Ti(H_2O)\}_2O]S_2O_6$[**]

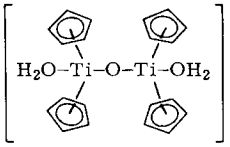
By *Ulf Thewalt* and *Gerhard Schleussner*[*]

Owing to its stability and the multiplicity of reactions which it undergoes with retention of the $(C_5H_5)_2Ti$ group, dichlorobis(η-cyclopentadienyl)titanium has proved to be one of the most important and preparatively useful complexes in organotitanium chemistry[1]. On reaction with NaX (X = Br, I, NO_3) in aqueous solution it affords dinuclear complexes, previously formulated as *(1)*[2].



(1a), X = Br
(1b), X = I
(1c), X = NO_3

However, when X is an oxoanion, as in *(1c)*, a structure of the type *(2)*, in which X and H_2O have exchanged their roles as ligands in the inner and outer spheres, is also plausible.



(2)

Organometallic compounds containing adjacent η-C_5H_5- and H_2O-ligands have—apart from postulated or incompletely characterized species—to our knowledge not been described in the literature.

We have now found by X-ray structure analysis of the salt *(2a)*, with 2X = dithionate and $n = 2$, that this complex can in fact be formulated as in *(2)*.

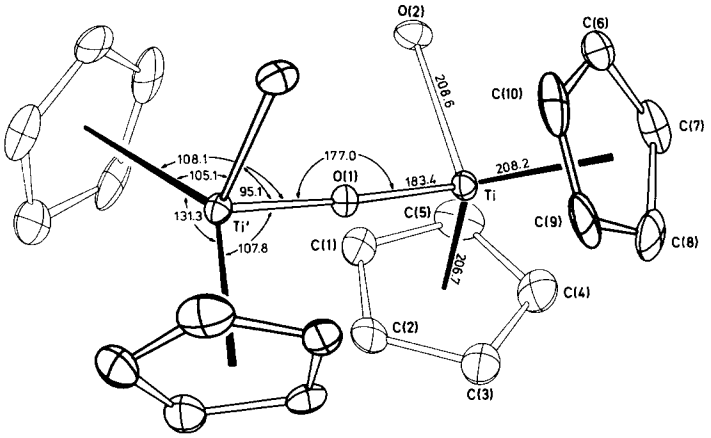


Fig. 1. The dinuclear cation of *(2a)*. The errors for the given bond lengths and angles are 0.5 pm and 0.3°, respectively. The figures quoted are with respect to the center points of the C_5H_5 rings. The angle Z(1)—Ti—O(2) is 103.3° [Z(1) = center of the ring containing C(1)].

The compound *(2a)* can readily be prepared by reaction of $(C_5H_5)_2TiCl_2$ and $Na_2S_2O_6 \cdot 2H_2O$ in water[3]. It forms hard, air-stable, orange-colored, short prismatic orthorhombic crystals[4]. As in $(C_5H_5)_2TiCl_2$[5] the Ti centers are surrounded by four ligands. One coordination position per Ti atom is occupied by a H_2O molecule. Both the $S_2O_6^{2-}$ anion as well as the complex cation occupy a special position in the unit cell: both exhibit exact C_2-2 symmetry, and their twofold symmetry axes coincide with the twofold symmetry axes determined by the space group. Figure 1 shows the cation with its essential bond lengths and angles. The Ti—O—Ti group is almost linear with a bond angle of 177°. The Ti—O—Ti angle in the corresponding compound $C_5H_5(Cl_2)TiOTi(Cl_2)C_5H_5$ is 180°[6]. The dihedral angle O(2)—Ti—Ti'—O(2) between the two halves of the complex is 74.1°. As in $(C_5H_5)_2TiCl_2$ the C_5H_5 groups are staggered.

(2a) and the complex with ClO_4^- as anion are the first organotitanium(IV) compounds displaying coordination of H_2O to a central Ti atom. This would suggest the complex formulated as in *(1c)* most likely has an analogous structure.

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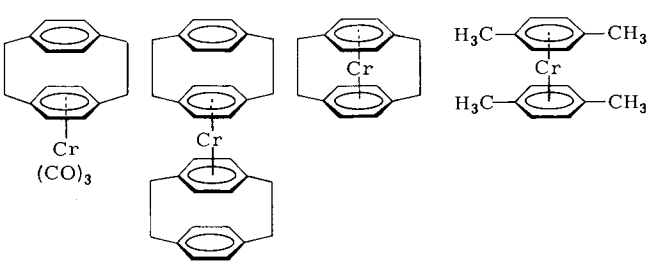
CAS Registry number:
$[\{(\eta\text{-}C_5H_5)_2Ti(H_2O)\}_2O]S_2O_6$, 66901-73-3

[1] *P. C. Wailes, R. S. P. Coutts, H. Weigold*: Organometallic Chemistry of Titanium, Zirconium, and Hafnium. Academic Press, New York 1974.
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[4] Space group Pbcn with $Z = 4$; lattice constants $a = 1582.7(4)$, $b = 1192.2(3)$, $c = 1215.2(3)$ pm; $d_{calc} = 1.646$, $d_{exp} = 1.64\ g \cdot cm^{-3}$. Determination and refinement of structure with 1261 structure factors [$F_0 > 2\sigma(F_0)$, Philips PW1100, $2\theta < 50°$, $\lambda = 71.069$ pm], $R_1 = 0.061$ (SHELX program: *G. M. Sheldrick*, unpublished.
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(η^{12}-[2.2]Paracyclophane)chromium(0)[**]

By *Christoph Elschenbroich, Reinhart Möckel*, and *Ulrich Zenneck*[*]

Cyclophanes could hitherto be coordinated to transition metals in combination with carbonyl ligands only (Example: *(1)*)[1].



(1) *(2)* *(3)* *(4)*

Of particular interest, however, are binary complexes of type *(2)* and *(3)*, since *(2)* is a potential building block for columnar structures of the composition [(η-cyclophane)-metal]$_n$, and *(3)* is expected to be very inert kinetically and

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[**] Metal-π-complexes of Benzene Derivatives, Part 9. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 8: *Ch. Elschenbroich, R. Möckel*, Angew. Chem. *89*, 908 (1977); Angew. Chem. Int. Ed. Engl. *16*, 870 (1977).

to display a change from intramolecular π-π repulsion (free ligand) to bonding η-arene-metal interaction (complex).

We have now cocondensed [2.2]paracyclophane with chromium atoms and obtained bis(η^6-[2.2]paracyclophane)chromium(0) *(2)*, (η^{12}-[2.2]paracyclophane)chromium(0) *(3)*, and oligomeric products according to the reaction

$$(C_{16}H_{16})_g + (Cr)_g \xrightarrow[\text{Cocondensation}]{-196\,^\circ C} (2) + (3) + \cdots$$

The complex *(3)* can be separated together with free cyclophane by sublimation (10^{-3} torr, 120 °C) and subsequently isolated in pure form *via* the redox system *(3)*/*(3)*$^+$[2]. The lability of *(2)*$^+$ towards solvolytic attack precludes the use of this method for the isolation of pure complex *(2)* from the residue left on sublimation. The presence of *(2)* can however be demonstrated mass spectroscopically (FD-MS: $m/e = 468$, $C_{32}H_{32}Cr^+ = M^+$) and by the ESR spectrum of *(2)*$^+$ (Table 1). The given structure of *(3)* follows from the appearance of two sharp singlets in the ^{1}H-NMR spectrum ([D]$_6$-benzene: δ = 2.64 (s, $H_{methylene}$), 4.63 (s, H_{arene}); int. 1 : 1), which are shifted upfield by 0.19 and 1.70 ppm, respectively, relative to free [2.2]paracyclophane; it is also in accord with the mass spectrum [70 eV: $m/e = 260$ (21 %, $C_{16}H_{16}Cr^+ = M^+$), 208 (13, $C_{16}H_{16}^+$), 156 (33, $C_8H_8Cr^+$), 104 (100, $C_8H_8^+$), 78 (12, $C_6H_6^+$), 52 (96, Cr^+)].

A comparison of the X-ray structure data of [2.2]paracyclophane (inter-ring C—C distance 278—309 pm[3]) with those of bis(η^6-benzene)chromium(0) (Cr-ring plane distance 161 pm[4]) would suggest that *(3)* represents a compressed sandwich complex. This manifests itself quite clearly in the ESR data of *(3)*$^+$, which are listed together with the corresponding data for *(2)*$^+$ and *(4)*$^+$ in Table 1.

Table 1. ESR data of the radical cations of *(2)*, *(3)* and *(4)* [a].

	⟨*g*⟩	$a(^1H_{arene})$ [G]	$a(^1H_{methylene})$ [G]	$a(^{53}Cr)$ [G]
(3)$^+$	1.9905	4.0 ±0.05 (8 H)	0.25 ±0.01 (8 H)	16.5 ±0.2
(2)$^+$	1.9865	3.55 ±0.05 (8 H)	[b]	18.5 ±0.2
(4)$^+$	1.9865	3.7 ±0.05 (8 H)	0.57 ±0.05 (12 H)	17.8 ±0.2

[a] Produced by air oxidation of the neutral complex dissolved in methanol and subsequent degassing. Recorded at −55 °C.
[b] Coupling not resolved.

In the case of *(3)*$^+$ the hyperfine coupling constants for the ring protons are greater and for ^{53}Cr smaller than in *(2)*$^+$ and *(4)*$^+$. This finding reflects a slightly more extensive Cr($3d_{z^2}$)→arene (σa_{1g}) spin delocalization in *(3)*$^+$, which is probably caused by a shorter metal-ligand distance than in *(4)*$^+$[5]; the smaller deviation in the isotropic *g*-factor from 2.0023 is also consistent with a smaller spin population at the central metal in *(3)*$^+$. On the other hand, the ESR data for *(2)*$^+$ closely resemble those for *(4)*$^+$, since a normal Cr-arene distance is possible in this case. It is tempting to explain the small differences of a (^{1}H) and a (^{53}Cr) for *(2)*$^+$ and *(4)*$^+$ in terms of a smaller Cr($3d_{z^2}$)-arene (σ, a_{1g}) overlap in *(2)*$^+$ due to the non-planar benzene rings of [2.2]paracyclophane orienting their convex sides towards the central metal atom. This concept could also serve to explain the surprisingly different reactivities of *(2)*$^+$, *(3)*$^+$, and *(4)*$^+$ in solvolytic metal-ligand cleavage. Whereas *(4)*$^+$ takes up an intermediate position, being indefinitely stable in methanol but being destroyed immediately by conc. HCl, *(2)*$^+$, on the one hand, slowly releases its ligands if dissolved in methanol at room temperature ($t_{1/2} \approx 8$ h, ESR) and *(3)*$^+$, on the other hand, is unaffected by conc. HCl over a period of weeks. The high stability of *(3)*$^+$ is explained by the fact that in this case the concave sides of the non-planar benzene rings of [2.2]paracyclophane, functioning as a rigid chelate ligand, are oriented towards the central metal, thus shielding the latter from solvolytic attack. In the case of *(2)*$^+$, however, the cleavage can take place in two steps *via* the half-sandwich complex (η^6-[2.2]paracyclophane)chromium$^+$, whereby the initial attack is easier than in *(4)*$^+$, because coordination *via* the convex sides of the non-planar benzene rings leaves the central metal atom exposed to attack by the solvent.

Procedure

Chromium (0.48 g) is evaporated from a Mo-wire (φ 1 mm) spiral (12 V, 44 A) in a 1 l reaction vessel (−196 °C, 10^{-4} torr) at the same time as [2.2]paracyclophane (2.5 g) from a heatable reservoir (1 V, 1.5 A, wall temperature ≈100 °C). The co-condensate is dissolved in warm toluene (+60 °C). Filtration, removal of the solvent by evaporation, and subsequent sublimation of the residue affords an ivory-colored material, which is then treated with 200 ml of toluene and 100 ml of water. The yellow aqueous solution obtained after brief passage of air is washed with 5 × 100 ml of toluene. To the washed solution is added 30 ml of toluene and 20 g each of KOH and $Na_2S_2O_4$ and the mixture stirred for 2 h. The yellow toluene solution is dried over KOH, the solvent removed, and the residue sublimed at 100 °C/10^{-3} torr. Approximately 10 mg (5 % based on unrecoverable ligand) of lemon-yellow *(3)* is obtained.—Ligand recovery: The residue from the first sublimation, which contains *(2)* as well as oligomeric complexes, is decomposed in air with 20 % KOH and extracted with 3 × 100 ml of toluene. From the combined extracts 2.25 g (90 %) [2.2]paracyclophane can be isolated.

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CAS Registry numbers:
(2)$^+$, 66901-75-5; *(3)*$^+$, 66901-74-4; *(3)*, 66901-71-1; *(4)*$^+$, 12242-82-9

[1] *D. J. Cram, D. I. Wilkinson*, J. Am. Chem. Soc. *82*, 5721 (1960); *F. Cristiani, D. De Filippo, P. Deplano, F. Devillanova, A. Diaz, E. F. Trogu, G. Verani*, Inorg. Chim. Acta *12*, 119 (1975); *H. Ohno, H. Horita, T. Otsubo, Y. Sakata, S. Misumi*, Tetrahedron Lett. *1977*, 265.
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Higher-Order Derivative Spectrophotometry for the Fine Resolution of UV/VIS Spectra

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Although various mechanical, optical and electrical methods have already been employed for some 25 years or more for

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recording derivative spectra (differentiation of signals)[1], derivative spectrophotometry itself is still in its infancy, but—thanks to the progress made in modern electronics—has now been in general use for more than 2 years. However, only first- and second-derivative spectra have so far been exploited. A closer study of these derivative spectra indicates that resolution of many hitherto unsolvable problems can only be realized by higher order differentiation of signals.

For this purpose we have developed an analog computer unit, with operational amplifiers, differentiators, separating modules and attenuators as well as active and passive filters, which enables the first analog on-line recording of low-noise, readily reproducible seventh order derivative spectra. The broad scope for variation of the differentiation time constants, attenuation, and critical frequencies, and the quality of the filters made it possible to adapt the apparatus to most problems presently at hand.

Investigations have shown that in most cases optimum resolution can be achieved with derivatives of the 4th order. As a rule all shoulders, terraces and inflection points of the unipolar signals are then transformed into bipolar signals and undesired background functions are eliminated. The signal-to-noise ratio can be kept low, thus enabling excellent reproducibility and quantitative evaluation.

We have tested this new method of higher-order derivative spectrophotometry (HODS method; $n > 2$) on a series of practical examples from various sectors of analytical chemistry and have obtained surprisingly good results. The areas of application which we have so far examined include: trace analysis (inorganic and organic), characterization of isomeric and homologous compounds, quality (purity) control, food analyses, drug analyses, clinical analyses, investigation of amino acids, peptides, proteins, nucleic acids, dyes and pigments, polymers *etc.*, measurements on turbid and deeply colored samples, on solids and gases, special applications in chromatography, reaction kinetics.

The efficiency of the HODS method becomes evident on examining the spectrum of Congo Red (Fig. 1). The absorption maximum of the azo dye lies in the visible spectrum region at 495 nm. Whereas very weak shoulders on the flanks of the absorption peak are barely recognizable in the fundamental spectrum, the superposed peaks become somewhat more discernable in the first and second derivative spectra, and very much more pronounced in the derivative spectra of third and fourth order. Derivatives of a still higher order do not provide any further important information in this particular example.

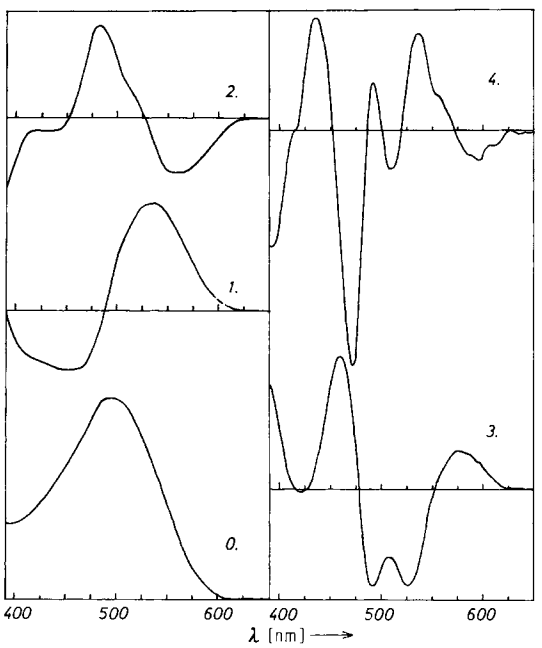


Fig. 1. Fundamental spectrum (below, left) and 1st to 4th derivative spectra of Congo Red; conc. 0.002% in water (water: scan 5 nm/s; range 2*E*).

More complex spectra show similar "fingerprints", as observed *e.g.* in IR spectroscopy. Trypsin and chymotryopsin, two proteases, which differ in the composition of their UV-active amino acids Phe, Tyr and Trp, both show a typical protein spectrum with a maximum at 280 nm and a minimum at 250 nm (Fig. 2a). The fundamental spectra differ very little from each other. However, the two proteins can be very easily characterized by their fourth derivative spectra. It can be seen from Figure 2b that the maxima and minima appear at almost the same λ values, but the amplitudes are different owing to the different proportions of Phe, Tyr and Trp. We are presently examining how far it is possible with this new method to determine various chromophores simultaneously and quantitatively.

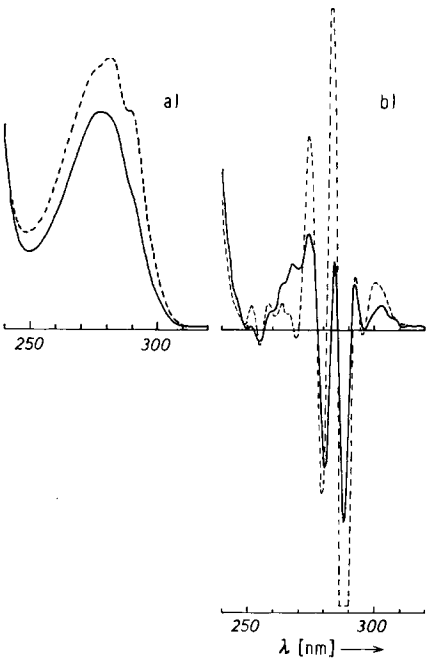


Fig. 2. a) Fundamental spectrum of bovine trypsin (——) and bovine chymotrypsin (– – –); conc. 0.05% in water (water; scan 2 nm/s; range 2*E*). b) 4th derivatives.

From the results so far it can be expected that the HODS method will greatly enhance the scope of UV-VIS spectrophotometry and provide new routes for the solution of analytical problems previously unresolvable by first- and second-derivative spectra[2].

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German version: Angew. Chem. *90*, 563 (1978)

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Complex Stabilization by Bifurcated Hydrogen Bonds: Bis[2-(*o*-methoxyphenoxy)ethoxyethyl] Ether-Thiourea[***]

By *Il-Hwan Suh* and *Wolfram Saenger*[*]

Cyclic, chiral crown ethers are of considerable interest because they form inclusion complexes with suitable ionic or neutral guest molecules and therefore can be used to separate racemic mixtures[1]. X-ray diffraction analyses have shown that such complexes are stabilized by $-NH_3^{\oplus}\cdots O$ or $C-H\cdots O$ interactions between the guest molecules and the cyclic crown ether oxygen atoms[2]. The steric limitations of complex formation imposed by cyclic crown ethers have been considerably reduced by preparing linear polyethers[3]. Recently, we have determined the structures of some complexes of metal ions with linear polyethers and found that the cations are coordinated with all the hetero atoms[4]. In order to determine what kind of interactions are involved we have now examined the 1:1 adduct of thiourea and bis[2-(*o*-methoxyphenoxy)ethoxyethyl] ether *(1)*[5].

(1) was recrystallized from acetone to yield flaky, yellowish crystals, m.p. 97—98 °C, space group Cc, cell constants $a=9.507$ Å, $b=21.200$ Å, $c=12.817$ Å, $\beta=95.61°$. 1197 X-ray diffractometer data were collected in the $2\theta/\omega$ scan mode using graphite monochromated MoK_α radiation. The structure was solved by direct methods and refined by full matrix least squares techniques to $R=2.9\,\%$ (Fig. 1).

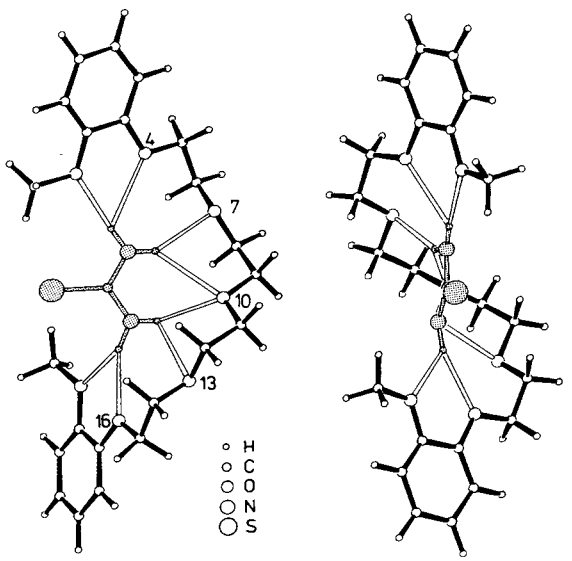


Fig. 1. Structure of complex *(1)*, viewed nearly perpendicular to the thiourea plane (left) and along the S···O(10) vector (right). Hydrogen bonds indicated by open lines, thiourea molecule shaded. H···O distances [Å] are, going from O(1) to O(19): 2.05, 2.64, [2.27, 2.41], 2.14, 2.71, [2.12, 2.39] (the numbers in brackets indicate bifurcated hydrogen bonds).

In complex *(1)* the thiourea molecule is hydrogen bonded through NH···O(ether) interactions with all seven oxygen atoms of the ligand, the central atom O(10) accepting two hydrogen bonds while the other six oxygen atoms accept one hydrogen bond each. The conformation of the polyether is such that it enables the thiourea molecule to utilize all the possible multidentate interactions offered by the partner. It does so without violating stereochemical restrictions, *i.e.* all torsion angles C—C—O—C and C—O—C—C along the polyether chain are *trans* while the angles O—C—C—O are *gauche*, as observed in a number of other linear polyether complexes with metal ions[6]. In these complexes, however, the ligands are wrapped more tightly around the small cation (radius ≈1 Å) in order to coordinate with all the donor atoms, while in case of the thiourea (radius ≈2 Å) the ligand has a more elongated configuration. In both types of complexes the host molecule recognizes the guest by means of a number of relatively weak interactions and fits itself to the geometry of the guest—a necessary and promising requirement for tailoring polyether ligands for certain specific purposes.

The hydrogen bonds formed in complex *(1)* are noteworthy because hydrogen bonds to ether oxygen atoms are only rarely observed, and here we even have bifurcated hydrogen bonds, which have previously been demonstrated with certainty only in very few cases[7]. These bonds, with N···O distances in the range between 3.059(5) Å and 3.258(5) Å, are longer than the hydrogen bonded N···O distances between amino (or imino) groups and keto oxygen atoms of *ca.* 2.90 Å, thus indicating the relative weakness of the hydrogen bond interactions involving ether oxygen atoms. The distances N(1)···O(10) [3.258(5)] and N(2)···O(10) [3.059(5) Å] differ in length, probably due to crowding in the "center" of the complex, while further out along the wings of the polyether chain the N···O distances are comparable for identically substituted oxygen atoms.

From X-ray studies hydrogen atoms cannot be located very accurately; therefore the NH-hydrogen atoms were fitted mathematically into "ideal" positions determined by a neutron diffraction study on thiourea[8]. Using the criteria outlined by *Donohue*[7], we find bifurcated hydrogen bonds with H···O distances shorter than the corresponding van der Waals distance, 2.60 Å, between N(1) and O(7), O(10) and between N(2) and O(16), O(19). Normal hydrogen bonds exist between N(1) and O(1), and between N(2) and O(10). No interactions (>2.6 Å) are evident between N(1), O(4) and between N(2), O(13) (cf. Fig. 1). This hydrogen bonding arrangement is valid only for the crystalline state. In solution, dynamic equilibrium will allow all the N—H hydrogen atoms to participate equally in bonding to the ether oxygen atoms.

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(1), 67030-89-1; thiourea, 62-56-6; bis[2-(*o*-methoxyphenoxy)ethoxyethyl] ether, 62107-75-9

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Directed Synthesis of $[Mo_3S_{13}]^{2-}$, an Isolated Cluster Containing Sulfur Atoms in Three Different States of Bonding

By *Achim Müller, Sabyasachi Sarkar, Ram Gopal Bhattacharyya, Siegfried Pohl,* and *Mechtild Dartmann*[*]

The directed synthesis of cluster-compounds is a current problem in transition metal chemistry[1]. For the subgroup VI metals (Mo and W) with d^n configuration, cluster types are expected to be dumb-bell shaped (in the case where $n=1$), triangular ($n=2$), tetrahedral ($n=3$) and octahedral ($n=4$) (here n also indicates the number of metal-metal bonds originating from each metal atom). Recently, the first binary species with $n=1$, *viz* $[Mo_2(S_2)_6]^{2-}$, has been isolated in the form of its ammonium salt[2]. We now report the synthesis of the homologous cluster with $n=2$ from a solution containing Mo^{IV}. Hitherto, the transition metal sulfur clusters, as model compounds of bioinorganic interest, could only be obtained by unusual reactions from unusual reactants and often only in low yield[3].

The dark-red, crystalline compound $(NH_4)_2[Mo_3S(S_2)_6]\cdot 1/2H_2O$ *(1)* is formed in aqueous solutions of molybdenum(IV) ions by treatment with polysulfide ions, and has been characterized by elemental analysis, DTA-, TG- and magnetic measurements, as well as by ESCA-, VIS-, IR- and Raman spectra, and a single-crystal structure analysis[4]. The salt is diamagnetic and the main IR absorption bands of the anion occur at 545 (m), 511 [m; ν(SS)], 459 [w; ν(Mo_3S)], 386 (w), 362 (w), 342 (m), 330 cm^{-1} [s; ν(MoS)] (assignments[5] by the use of ^{92}Mo- and ^{100}Mo-isotopes). The compound is extraordinarily stable and is not even decomposed by hydrochloric acid. It is almost insoluble in water and is only moderately soluble in dimethylformamide.

Like $[Mo_2^V(S_2)_6]^{2-}$[2] the new cluster $[Mo_3^{IV}S_{13}]^{2-}$ also contains both terminal and bridging disulfide groups (Fig. 1), and the equivalent bonds in both the anions have roughly

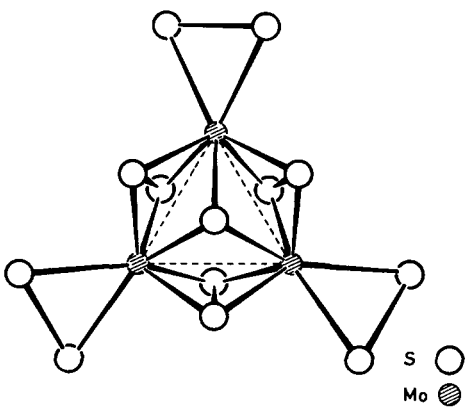


Fig. 1. Structure of the cluster $[Mo_3S_{13}]^{2-}$ in crystals of *(1)* [schematic].

the same length[2]. As expected, the Mo—Mo distances (2.67 Å) are somewhat shorter in *(1)* and the coordination number of molybdenum is again 9[4].

The S_2^{2-} ligands favor high coordination numbers and are suitable for stabilizing metal clusters, since an optimum shielding of the metal atoms is achieved through the high coordination numbers arising due to the small MS_2-angle. From the above mentioned scheme the existence of the homologous cluster $[Mo_4^{III}S_4(S_2)_4]^{4-}$ could be predicted[6]. Obviously the stability of these compounds is also connected with the occurrence of only tricoordinated sulfur in the central units $\{Mo(S_2)_2Mo\}$[2], $\{Mo_3S(S_2)_3\}$ (in *(1)*) and probably $\{Mo_4S_4\}$[6] (for the low reactivity cf. [3]).

Experimental

30 ml of saturated ammonium polysulfide is added to a reddish brown solution of 2.0 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 1.5 g of $NH_2OH\cdot HCl$ in 30 ml water. The resulting solution is warmed to 40—50 °C for 1 h, then cooled to room temperature, filtered, and the filtrate heated at *ca.* 90 °C for 3—4 h. Dark-red crystals of *(1)* then separate. The crystals are washed with $(NH_4)_2S_x$, H_2O, ethanol, CS_2 and ether; yield: 0.5 g. *(1)* can also be obtained directly by adding $MoCl_4(C_5H_5N)_2$ to a polysulfide solution (the high tendency of formation is comparable with that of $(NH_4)_2[Mo_2(S_2)_6]\cdot 2H_2O$).

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$(NH_4)_2[Mo_3S(S_2)_6]$, 67031-31-6; $(NH_4)_6Mo_7O_{24}$, 12027-67-7; $(NH_4)_2S_x$, 9080-17-5

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[4] Details of the X-ray structure analysis will be published later. The water content follows from elemental analysis and TG but could not be finally confirmed by structure analysis.
[5] Because of the coupling in the ring system the designation of the vibrations is only approximate.
[6] The central unit has already been found in $[(C_5H_5)MoS]_4$ (cf. [3]).

Optically Active Polyvinyl Compounds with Chirality in the Main Chain[**]

By *Günter Wulff, Karl Zabrocki,* and *Johann Hohn*[*]

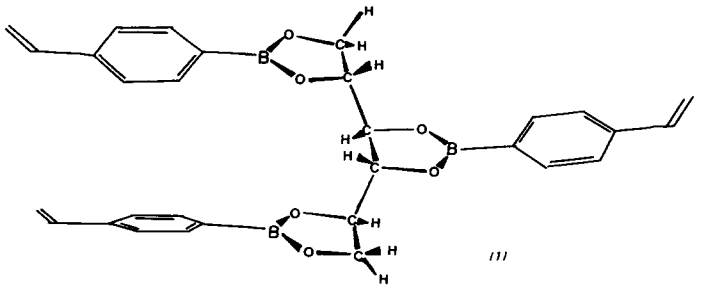
We recently described a method for the preparation of synthetic polymers having cavities containing functional groups in a definite steric arrangement[1,2]. Functionally substituted polymerizable vinyl compounds were bound to a suitable chiral template molecule and then copolymerized under stringent crosslinking conditions. After removal of the template from the polymer the latter contains microcavities, whose shape is largely determined by the shape of the template, and within which the functional groups are in a fixed stereochemistry corresponding to the structure of the template. Such polymers can be used for the resolution of racemates[2].

In order to clarify whether the asymmetry of the microcavities is due only to an asymmetric crosslinking of the polymer, or also to chiral regions in the linear chains, we used for our investigations the previously described monomer *(1)*[1,3] with D-mannitol as template and copolymerized it by radical initiation together with methyl methacrylate (molar ratio 16:84) in benzene, but this time without the addition of a further crosslinking agent.

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(1)

After removal of the crosslinking template D-mannitol, we now obtained a soluble copolymer of *p*-vinylphenylboronic acid and methyl methacrylate with a monomer ratio of 1:2 (average molecular weight $\bar{M}_n = 120000$, membrane osmometric). The copolymer had an optical activity of $[\alpha]_{365}^{20} = -29.4°$ ($\alpha = -0.123 \pm 0.002°$, acetone/water 9:1, $c = 0.42$) [monomer *(1)*: $[\alpha]_{365}^{20} = +270$ (chloroform)].

In order to prove that incorporation or incomplete removal of D-mannitol was not responsible for the observed optical activity, the experiment was repeated with ^{14}C-labeled D-mannitol. We found that only 0.2% of the total D-mannitol was still present in the polymer, thus ruling out the possibility of it having any notable influence on the optical rotation. Moreover, addition of D-mannitol to polymer solutions was found to lead to a change in the rotation to positive values until precipitation of the polymer due to progressive crosslinking by the mannitol.

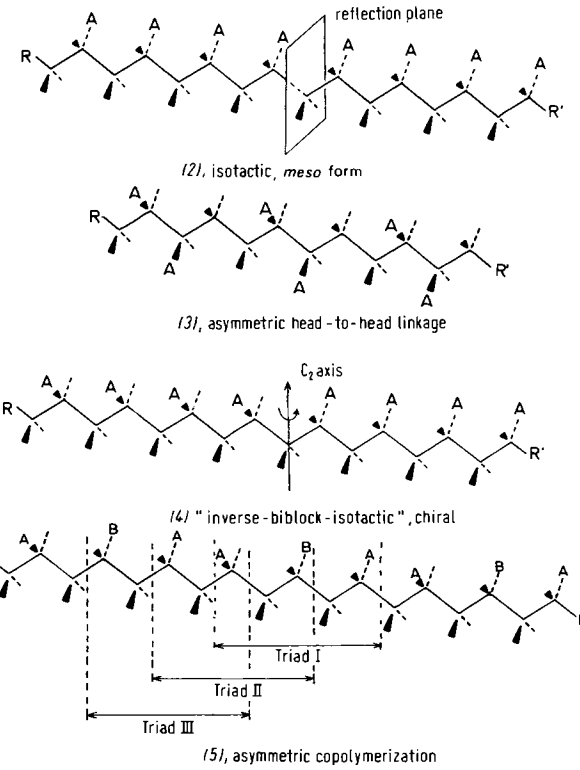
From these findings we conclude that our copolymer of 1-substituted olefins possesses chirality localized in the main chain by asymmetric induced polymerization. Optically active polymers or copolymers of 1-substituted olefins were previously unknown—excepting those having chirality centers in the side-chains[4]. According to the literature[4, 5] optical activity is not expected to occur in polyvinyl compounds, since in each step of the polymerization of a 1-substituted olefin a chiral center is formed from a prochiral center but in atactic polymers, with irregularly, in syndiotactic with regularly alternating *R*- and *S*-configuration. Chains of this type could indeed be chiral, but the optical activity is intramolecularly compensated and therefore is not measurable. Isotactic polymers *(2)*[6] could begin with an *R*- or with an *S*-configuration with formation of two enantiomorphic chains. If, however, the difference in the end groups can be neglected ($R—CH_2- \cong —R'$), as is always permissible in the case of longer chain lengths, the molecule possesses a symmetry plane (*meso* form) and does not show any optical activity[4].

On the other hand, for polymers with 1,2-substituted segments, which are obtainable *e.g.* from cyclic olefins such as maleic anhydride, the occurrence of chirality in the main chain is to be expected[5a], and numerous optically active polymers have already thus been obtained by asymmetric induction[4].

We should like to discuss here how also optically active polyvinyl or polyvinylidene compounds with chirality in the main chain can occur, and thus offer an explanation for the optical activity observed by us.

One possibility would be by head-to-head polymerization of the monomers *(3)*, in which 1,2-disubstituted chiral segments can be formed, as in the case of 1,2-substituted monomers. However, in the case of the monomers used by us such a manner of polymerization can be ruled out.

Chirality in the main chain would also be possible if the substituents near the center of the chain in an isotactic polymer chain change to the other side of the main chain *(4)* with respect to the Fischer projection. Since each part of the chain



has in itself a strong isotactic structure, we propose for this type of arrangement the designation "inverse-biblock isotactic". It should be pointed out that in an "inverse-biblock isotactic" chain the configuration of all asymmetric C atoms remains the same, whereas in a strictly isotactic chain it changes in the middle from *R* to *S*. With identical chain ends *(4)* has only one twofold symmetry axis and is therefore chiral as a whole.

While the concept "inverse-biblock isotactic" applies for both uni- as well as co-polymers, there should also be a type of chirality of polymer chains which can occur only in copolymers. *(5)* represents an example of several possibilities. In this copolymer the three different triads I, II and III are asymmetric.

It must be decided whether in our case the optical activity is due to an "inverse-biblock isotactic" structure or to an asymmetric copolymerization. Moreover it must be remembered that optical activity can already occur if such structures are only partially realized in the chains.

In the case of "inverse-biblock isotactic" structures, a unipolymer must also be optically active, so we tried to synthesize optically active poly(*p*-vinylphenylboronic acid). *(1)* was polymerized and the mannitol subsequently removed; or *(1)* and *p*-vinylphenylboronic acid glycol ester were copolymerized

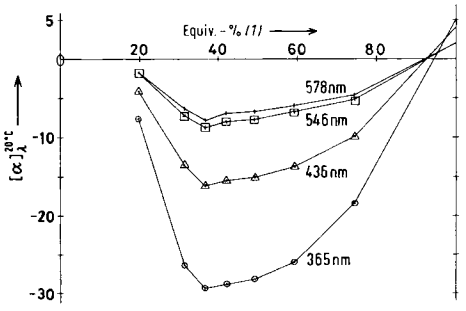


Fig. 1. Specific optical rotation of copolymers of methyl methacrylate and *(1)* after removal of D-mannitol. Equiv.% *(1)* (1 equiv. *(1)* = 1/3 mol *(1)*) in the polymerization mixture and rotation of various wavelengths are given.

and the mannitol and glycol removed. The polymers obtained, however, showed no significant optical activity. Further indications were given by the copolymerizations of methyl methacrylate with varying amounts of *(1)*. The specific rotation of these copolymers after removal of the mannitol is strongly dependent upon the molar ratio of the comonomers (cf. Fig. 1), the maximum negative rotation being reached at 16 mol-% *(1)* (36 equiv.% boronic acid groups). This means that a definite composition of the copolymerization mixture corresponds to the highest asymmetric induction. We also obtained copolymers with negative rotation after removal of D-mannitol on using styrene as comonomer of *(1)*.

These results suggest the likelihood of an asymmetric copolymerization which can be explained in terms of the spatial structure of *(1)*: A methyl methacrylate molecule could be introduced stereo- and enantiospecifically in the chain between each two *p*-vinylphenylboronate moieties in the 1,2- and 5,6-positions of the mannitol, with asymmetrical triads being formed as in Formula *(5)*, Triad I.

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Directed Cooperativity and Site Separation of Mercapto Groups in Synthetic Polymers[1]

By *Günter Wulff* and *Ilona Schulze*[*]

With the aid of chiral template molecules it has been possible to prepare polymers having chiral cavities which contain functional groups in definite stereochemical arrangement[2]. The ability of such polymers to separate racemates might depend upon the asymmetric structure of the cavities[3] and the exactness of orientation of the functional groups. In order to acquire more detailed information about the influence of the stereochemistry of the functional groups on the specificity we sought a model system which is sensitive only to the distance between the functional groups.

For this purpose bis(*p*-vinylbenzyl) disulfide *(1)*[4] was copolymerized under various conditions with styrene and divinylbenzene. On polymerization the two vinyl groups of the disulfide *(1)* ought to be incorporated at various positions of a growing chain or in various chains ("discontinuate words" arrangement[2a]). If the disulfide bridges are reductively transformed into mercapto groups then they should remain in a definite related position to each other in a strongly cross-linked polymer (cf. Fig. 1).

Since mercapto groups can be selectively re-oxidized to disulfides[5], retention of this spatial relationship can be quantitatively determined on the basis of the re-oxidized portion (degree of re-oxidation).

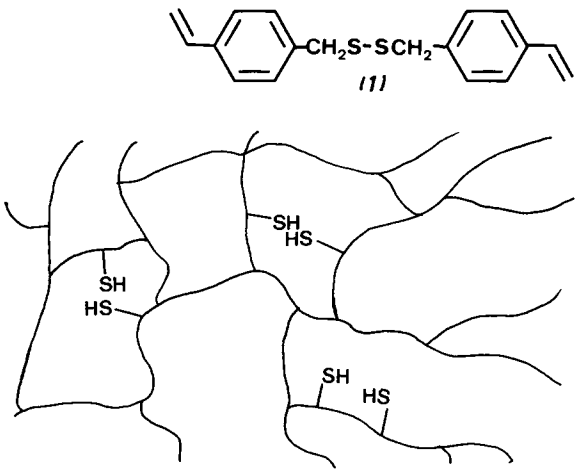


Fig. 1. SH-groups in definite stereochemical arrangement by polymerization of *(1)*.

For an exact assessment, however, comparison is necessary with a polymer which contains the mercapto groups in the same concentration but in a random distribution (Fig. 2). Polymers of this type were obtained from *p*-vinylbenzyl thioacetate *(2)*[6]. On complete site separation of the mercapto groups no reoxidation of these polymers should occur.

Table 1 lists the composition of the monomeric mixtures used for the preparation of the polymers. Using the two monomers a total of three series of polymers were prepared having as far as possible comparable polymeric properties and containing the same amounts of sulfur. A complete comparability is not to be expected owing to the different polymerization properties of a mono- and a difunctional monomer.

Table 1. Percentage composition of the monomer mixture used for preparation of the polymers [a].

Monomers	Polymers					
	A1	A2	B1	B2	C1	C2
(1) (mmol *(1)* per g)	24.2 (0.81)	—	20.2 (0.68)	—	2.3 (0.077)	—
(2) (mmol *(2)* per g)	—	24.7 (1.30)	—	26.7 (1.28)	—	2.9 (0.15)
Styrene	75.8	72.5	—	—	7.2	7.2
Divinylbenzene (techn.)	—	2.8	79.8	73.3	90.5	89.9

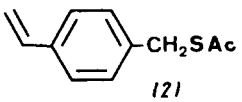
[a] In each case the quoted monomer mixtures (in wt-%) were polymerized in the presence of the same volume of acetonitrile/toluene (2:1) with azobis(isobutyronitrile) for 7d at 50°C.
Polymers B1, B2, C1 and C2 were macroporous

Table 2. Properties of the polymers.

	Polymers					
	A1	A2	B1	B2	C1	C2
% SH-Groups [a]	97	97	68	96	95	96
Degree of reoxidation [b]	99	69	98	33	95	<5

[a] Percent sulfur present as —SH after treatment with diborane. SH-groups determined by titration with $AgNO_3$ in isopropanol [7]. Total sulfur content determined by elemental analysis.
[b] Percent SH-groups that could be reoxidized with I_2 in methanol.

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(21)

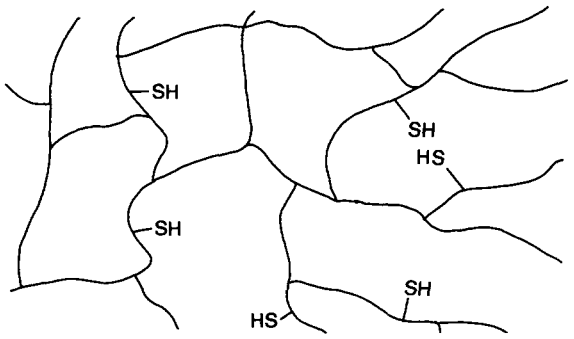


Fig. 2. SH-groups in random distribution by polymerization of *(2)*.

The polymers were prepared by free-radical copolymerization of the monomers *(1)* and *(2)* with varying amounts of styrene and divinylbenzene as crosslinking agent in acetonitrile/toluene (2:1). For both types of polymers the reductive generation of the SH-groups was carried out with diborane ($NaBH_4$ and $AlCl_3$)[7] in diglyme. In this way more than 90% of the total sulfur present in the polymer (except in the case of polymer B1) could be converted into SH-groups (see Table 2). This finding shows that chain-transfer reactions, possible in the case of disulfides and thioacetates, do not occur to any appreciable extent.

The reoxidation of the SH-groups was carried out with iodine in methanol[5] (Table 2). Polymers with less crosslinking exhibited higher degrees of reoxidation, being still 69% even in the case of polymer A2. Apparently the polymer chains retain considerable flexibility, making reactions possible also in the case of randomly distributed SH-groups over a particular distance. Remarkably, however, 33% reoxidation has been observed even in highly-crosslinked polymers from monomer *(2)* (polymer B2). But the reaction kinetics are noticeably different to those in the case of polymer B1. Whereas 98% oxidation was achieved within 1.5 h in the case of polymer B1 the ultimate degree of oxidation of polymer B2 was reached only after about 30 h. The incomplete site separation observed for the polymer B2 is in agreement with the experiments of other authors concerning site separation of functional groups in polymers. *Crowley* and *Rapoport*[8] recently correlated these findings and came to the conclusion that almost all previous attempts to achieve complete site separation were not very successful.

When the concentration of the SH-groups on the polymer in our experiments was reduced about tenfold, oxidation was no longer possible in the case of polymer C2 with randomly distributed SH-groups, *i.e.* complete site-separation could be achieved. Under the same conditions the analogously prepared polymer from monomer *(1)* then showed 95% oxidation. This comparison clearly indicates that practically all SH groups in the polymer C1 remain at a distance from a second SH-group allowing reoxidation to the disulfide. The degrees of oxidation are strongly dependent upon the swelling ability of the solvent used in the oxidation. Thus the degree of reoxidation of polymer B2 in the strongly swelling solvent toluene increased owing to the better mobility of the chains. In contrast, the degree of reoxidation of polymer B1 in the same solvent decreased, since apparently the separation between the two groups is considerably increased by the swelling. Thus the method described here permits investigation of the influence of several parameters on the stability of the functional groups in a "discontinuate words" arrangement[9]. Moreover, it is also possible to determine quantitatively the site-separation of functional groups on polymers. Especially interesting is the possibility of introducing functional groups (in our case two SH-groups) in a definite cooperativity in a polymer. Such polymers can be used as redox resins and serve as models for enzymes containing SH-groups.

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(1), 67030-83-5; *(2)*, 67030-86-8; styrene, 100-42-5; divinylbenzene, 1321-74-0; A1, 67030-84-6; A2, 67030-87-9; B1, 67030-85-7; B2, 67049-40-5; C1, 67030-88-0

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A New High-Pressure Phase of Barium Disilicide[**]

By *Jürgen Evers, Gilbert Oehlinger*, and *Armin Weiss*[*]

The isolated Si_4 tetrahedra present in the orthorhombic normal-pressure(NP)-phase[1] of barium disilicide can be transformed into corrugated Si layers of the trigonal $EuGe_2$-type[2] by high-pressure/high-temperature treatment. Surprisingly the polymerization can also lead to a regular three-dimensional Si network. This new high-pressure(HP)-phase of $BaSi_2$ is metastable at normal pressure; it is obtained if the orthorhombic modification is heated to 600—800°C at 40 kbar in a belt apparatus[3] and then quenched to room temperature under pressure. The silvery to golden compound is stable in the absence of air and moisture. Complete retransformation into the phase with isolated Si_4 tetrahedra takes place, when it is heated to approximately 400°C at normal pressure.

The powder diagram of the new HP-phase can be indexed cubic showing the characteristic sequence of reflections for the $SrSi_2$-type structure[4]. The intensities are also consistent with this type of lattice. The best agreement between observed and calculated intensities (24 reflections, $Mo_{K\alpha}$ radiation) was obtained for the positional parameter $x_{Si}=0.419$ (reliability factor $R=0.087$). The crystallographic data of the cubic, trigonal and orthorhombic modifications of $BaSi_2$ are listed in Table 1.

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Table 1. Comparison of the crystallographic data of the three modifications of barium disilicide.

	New HP-Phase	HP-Phase [2]	NP-Phase [1]
Symmetry	cubic	trigonal	orthorhombic
Space group	O^{6}- $P4_332$ (or O^{7}-$P4_132$)	D_{3d}^{3}-$P\bar{3}m1$	D_{2h}^{16}-Pnma (or C_{2v}^{9}-$Pna2_1$)
Axes [pm]	$a=671.5\pm0.5$	$a=404.7\pm0.3$ $c=533.0\pm0.5$	$a=892\pm6$ $b=675\pm6$ $c=1157\pm6$
Cell volume [pm³]	302.8×10^6	75.6×10^6	$696.6\cdot10^6$
Density [g/cm³]			
obs.	4.2_7	4.2_6	3.54
calc.	4.246	4.251	3.68
Number of formula units	4	1	8
Atomic positions	4 Ba in 4a 8 Si in 8c	1 Ba in 1a 2 Si in 2d	4 Ba_I in 4c 4 Ba_{II} in 4c 4 Si_I in 4c 4 Si_{II} in 4c 8 Si_{III} in 8d

The $SrSi_2$-type structure has hitherto been reported for $SrSi_2$(NP) itself only. The cubic modification of $BaSi_2$(HP) is the second binary representative of this lattice type. Its Si sublattice is built up of very flat trigonal pyramids, rotated against each other, thus forming a three-dimensional array. The cavities within the skeleton contain the metal atoms. The characteristic feature of this lattice type is the three-dimensional network of only tridentate silicon. The ideal Si sublattice of this structure ($x_{Si}=0.375$) with three-bonded atoms is the analog to the diamond lattice with four-bonded atoms[5].

The number of nearest neighbors, their bond distances and the $Si^{Si}Si$ bond angles of the cubic and the trigonal HP modifications of $BaSi_2$ are compared in Table 2. The nearest distance between the three-bonded Si atoms is 245 pm; it is the same in both HP phases. The $Si^{Si}Si$ bond angle in the trigonal phase is larger than in the cubic phase.

Table 2. Nearest neighbors, bond distances, and $Si^{Si}Si$ bond angles of the two high-pressure modifications of barium disilicide.

	Cubic	Trigonal
Ba neighbors	6 Ba 411 pm	6 Ba 405 pm
		2 Ba 533 pm
	6 Si 337 pm	6 Si 328 pm
	2 Si 342 pm	6 Si 382 pm
Si neighbors	3 Si 245 pm	3 Si 245 pm
	3 Ba 337 pm	3 Ba 328 pm
	1 Ba 342 pm	3 Ba 382 pm
∢ SiSiSi	$118.2°$	$111.6°$

In a very formal interpretation of the structure as $Ba^{2+}(Si^{-})_2$ according to the Zintl-Klemm-Bussmann concept each Si atom would have five valence electrons. Of these, three would be required for bonding to the three Si neighbors. If the two remaining electrons were to act as a "lone pair", the $Si^{Si}Si$ bond angle would approach that of the tetrahedral angle. On the other hand, if they were to participate in the bond system, coplanar triangular groups would be expected. In the trigonal modification the Ba—Ba and the Ba—Si bond lengths (Table 2) are slightly smaller than in the cubic modification. The coordination in the cubic phase is 8:4 (Ba has 8 Si neighbors, Si has 4 Ba neighbors), in the trigonal phase 12:6. Surprisingly, the higher coordination in the trigonal phase is not reflected in its density (Table 1); both the cubic and the trigonal polymorph are 13% more densely packed than the orthorhombic phase.

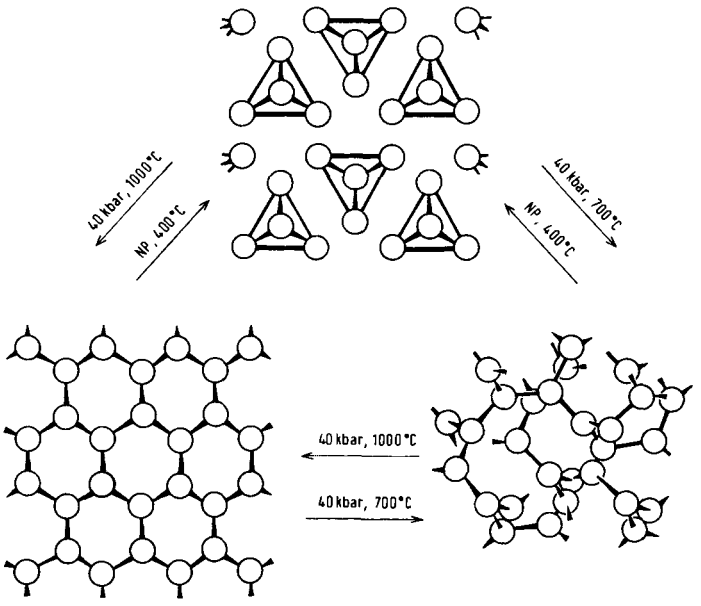


Fig. 1. Transition scheme between isolated Si tetrahedra, corrugated Si layers and three-bonded Si skeleton in barium disilicide.

The relations between isolated Si_4 tetrahedra, corrugated Si layers and the three-dimensional Si network are schematically shown in Figure 1.

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CAS Registry number:
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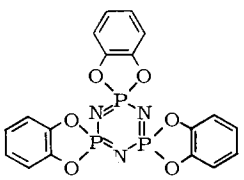
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This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

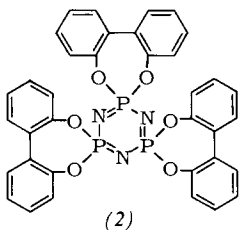
The role of cerebroside sulfate as opiate receptor is discussed in an article by *H. H. Loh, P. Y. Law, T. Oswald, T. M. Cho*, and *E. L. Way*. Cerebroside sulfate possesses most of the properties required of an opiate receptor, namely high affinity and the ability to bind stereoselectively. Although these findings still do not allow proof of identity, it is most likely that some interrelationship exists. Cerebroside sulfate is a component of brain tissue, and a partially purified opiate receptor from mouse brain proved to be chemically the same as cerebroside sulfate. Further investigations showed that reduction in the availability of cerebroside sulfate was accompanied by a decrease in analgesic action of morphine and the number of binding sites. [Possible Involvement of Cerebroside Sulfate in Opiate Receptor Binding. Fed. Proc. *37*, 147—152 (1978); 36 references]

[Rd 25 IE]

In cyclophosphazene clathrates the guest molecules are located in a tunnel, the dimensions of which are dependent upon the substituents of the host molecule. *H. R. Allcock* surveys this field. The parent molecule *(1)*, which was discovered by chance to act as a host molecule, forms planar aggregates of three molecules at a time. The next layer is twisted in such a way that a tunnel of 4.5—5 Å diameter is formed which can accept, *e.g.*, benzene. *(1)* is suitable for separating mixtures of, say, heptane and cyclohexane as well as *m*-xylene, *p*-xylene, and ethylbenzene. The analog of *(1)* obtained from 2,3-naphthalenediol also forms clathrates; the tunnel has a diameter of 9—10 Å. As shown for compound *(2)* which does not form clathrates, it is the shape of the molecules of this series which is responsible for their properties. [Cyclophosphazene Clathrates—Exploring the Adjustable Tunnel. Acc. Chem. Res. *11*, 81—87 (1978); 33 references]



(1)



(2)

[Rd 21 IE]

The identification and regulation of α- and β-adrenergic receptors form the subject of a review by *R. J. Lefkowitz*. Methods for the direct binding of radioactive ligands to α- and β-adrenergic receptors have been developed in the course of the last few years. Radioactively labeled adrenergic antagonists or agonists are used in order to identify receptors in the membrane fractions of catecholamine-sensitive tissues. In the case of β-adrenergic receptors the close relationship between binding and activation of adenylate cyclase simplifies identification. Such direct receptor-binding investigations provide further useful information about the molecular and regulatory properties of receptors. [Identification and Regulation of Alpha- and Beta-Adrenergic Receptors. Fed. Proc. *38*, 123—129 (1978); 87 references]

[Rd 23 IE]

Affinity-labeling of estrogen receptors is the subject of a report by *J. A. Katzenellenbogen*. As shown by competition experiments, estradiol and hexestrol derivatives bearing photoreactive diazocarbonyl or azide groups exhibit receptor-binding activity, and, after irradiation, inactivate the receptor. In unpurified uterus specimens other proteins besides the receptor are labeled. From previously purified specimens a photolabeled product can be isolated which shows all the properties of an estrogen receptor. [Photoaffinity Labeling of Estrogen Receptors. Fed. Proc. *37*, 174—178 (1978); 28 references]

[Rd 24 IE]

BOOK REVIEWS

Elektrolytgleichgewichte und Elektrochemie (Electrolyte Equilibria and Electrochemistry). Fachstudium Chemie, Arbeitsbuch 5. By *E.-G. Jäger, K. Schöne* and *G. Werner*. Verlag Chemie GmbH, Weinheim—New York, 1977, 1st edit., 308 pp., 64 figs., numerous tables, paper, DM 34.00.

The present volume is part of a comprehensive work intended to provide chemistry students with the necessary fundamentals. Textbooks and workbooks serve as an aid to self-study, tutorials, and practicals.

The introductory text contains a number of basic questions following a short presentation of the problem. The aim is to check whether the student has understood the corresponding section in the textbook. This section is followed by instructions for practical experiments and calculation exercises, the solutions to which are given at the end of the book.

The present volume deals mainly with electro-analytical applications of electrochemical equilibria. Problems of kinetics are only briefly touched upon in the introductory chapter on the fundamentals, where the authors discuss the conductivity of electrolyte solutions, reversible cell potentials, and polarization when a current is flowing, together with experimental methods. The other chapters consider various equilibria (redox, acid-base, complex, precipitation, extraction, and ion-exchange), methods for the determination of equilibrium constants, and the corresponding analytical methods, such as redox titrations, complexometry, and gravimetry.

The book conveys sound basic knowledge. In a few cases the terminology is not quite appropriate: *e.g.* "depolarizer", or "resistance capacity" of a conductivity cell (instead of cell constant). Some definitions could be improved (*e.g.*, not every

cell through which no current flows is in equilibrium). In another place, the wrong impression is given that corrosion depends only on local cell action. It is particularly regrettable in a modern textbook that the IUPAC recommendations for definitions and nomenclature are often ignored. Apart from such minor shortcomings, however, this book should prove a valuable study aid that will find many friends, not least because it is reasonably priced and well presented.

K. E. Heusler [NB 431 IE]

Biophysik—ein Lehrbuch (Biophysics—A Textbook). Edited by *W. Hoppe, W. Lohmann, H. Markl,* and *H. Ziegler.* Springer-Verlag, Berlin—Heidelberg—New York 1977. 780 pp., 640 figs., bound, DM 98.—.

The title of this book, which contains contributions by fifty-two experts, inevitably poses the question: "What is biophysics?" Since animate and inanimate nature obey the same laws, biophysics cannot be understood as a science *sui generis.* However, living processes can be treated physically, just as there are genetic and chemical ways of consideration, and it is as such that biophysics surely wants to be known. Each of these modes of treatment has given birth to its own tools and techniques. Since more and more physicists are turning to biology, and physical methods are used increasingly to understand life processes, there is bound to be an interest in a textbook explaining the mode of thinking and the physical laws and techniques that have decisively contributed to the solution of biological problems and have introduced an eminently fruitful development, though admittedly this is credited to molecular biology rather than to biophysics. The present attempt at writing a textbook on biophysics has unfortunately been unsuccessful, because the basic biological concept is missing. There is no guiding principle that could tie together the many jewels that occur in this book in a clear and logical manner. Without such a thread of Ariadne the reader soon gets lost in a maze of problems that appear to lead an isolated life of their own. The editors must be given the credit of anticipating these difficulties and trying to overcome them. They therefore decided to incorporate "supplementary scientific material" taken from biology in concentrated form, though this was bound to remain a patching-up operation. The core of the book should have been made up of topical problems in biology, and some of these are indeed dealt with. Physics and physical chemistry should then have provided the requisites for describing these topical biological problems in physical and physicochemical terms, for analyzing them, and for making them comprehensible. Only thus would an unfortunate intermixing of physics, chemistry, and biology have been avoided.

The book begins by describing the cell, nucleic acids, and proteins. *Walter Hoppe, Brunner* and *Dransfeld et al.* then describe physical methods, namely X-ray and electron diffraction and light scattering in detail and searchingly—in fact uniquely in this form. It was these methods that elucidated the structure of biological molecules and made possible a study of biology on the molecular level. However, one misses the cornerstones of molecular biology, which are only offered later in Chapters 9 and 10 by *Huber* and *Zillig* as "supplementary scientific material". A possible criticism is the emphasis given to the discussion of various physical methods for the investigation of biological molecules (Chapter 3). For example, IR and more especially Mössbauer spectroscopy are described in greater detail by *Kalvius* and *Parak* than the methods of nuclear magnetic and electron spin resonance. I doubt whether the student will really understand how important these methods were for the elucidation of membrane structure or enzyme catalysis, for example, when reading about resonance spectroscopy. The fundamental Chapter 4 on intramolecular and intermolecular interactions *(Hofacker, Ladik)* reinforces my view that physical and physiochemical aspects are best described by physicists, physical chemists, and theoretical chemists, who would hardly describe themselves as biophysicists. A competent treatment suffices for the demands of the chemists and physicists just a much as it teaches the molecular biologists. I am here including the contributions by *Hans Kuhn* and *Friedrich Dörr* about energy-transfer mechanisms (Chapter 5) and thermodynamics (Chapter 8). These contributions, including the already discussed Chapters 3 and 4, could have been made into an excellent textbook of physics and physical methods for biologists and biochemists. For the reader interested in membrane structure and function Chapter 11 is a source of valuable but not easily digested information. Certain carefully selected examples from Chapter 12 (receptor transduction) and Chapter 13 (photophysics, photochemistry, and bioenergetics) might have merited consideration, but such a degree of heterogeneity is hardly justified. Bioenergetics could have been a central theme, but then the physical principles would have had to be coordinated better with the biological and biochemical phenomena. Photobiology could have been followed by a selective treatment of physical influences on life processes (cf. Chapters 15 and 16), because what hides under the term "biomechanics" (Chapter 14, pages 503—600) are system physiology and engineering applied especially to biological locomotion. Like routine methods (use of isotopes) and special fields such as radiation physics (Chapter 6) this should have been left to relevant handbooks. The up-to-date and readable treatment of the molecular biology of muscle contraction by *Mannherz* and *Holmes* is amiss in this chapter; it ought to have been coordinated with *Huber*'s contribution to reinforce the relationship to molecular biology. The last two chapters, on Cybernetics (Chapter 17 by *Marko, Creutzfeldt* and *Reichardt*) and Evolution (Chapter 18), are undoubtedly part of the central theme of present-day biology. They open up fascinating insights into complex biological systems (for example the flight orientation of flies by *Reichardt*) and the evolution of biological systems *(Hans Kuhn).* (The Eigen theory of evolution is presented by a well-known, already published, popular introduction by *Peter Schuster.*) There was a splendid opportunity here of awakening an understanding of where the boundaries of physical knowledge about nature lie if these contributions had been put at the center of the physical considerations and analysis together with ones about structure and function of biopolymers (proteins and nucleic acids) and membranes as main biological reference points. The whole would then have become better than its parts and not the parts better than the book as a whole.

The editors have made little effort to critically edit and coordinate the individual contributions, and they emphasize this themselves in the preface. Unfortunately, they cannot be praised for this laissez faire attitude. The biologist is going to find it difficult to recognize the relationships to physics, currently so topical, and the physicist and the chemist are going to miss the biological relationships which help them to understand the laws of the make-up and function of living systems, the "logique du vivant" as *François Jacob* puts it. What remains is a mixture of essays about physics, chemistry, and biology, some of which are so good that despite all reservations they can be recommended with good conscience. Sadly, the textbook as such cannot be recommended.

Ernst J. M. Helmreich [NB 420 IE]

Reaction Mechanisms in Organic Chemistry. By *F. Badea.* Abacus Press, Tunbridge Wells 1977. 1st Edit., 701 pp., numerous figs., bound, £ 18.85.

The author attempts to provide a comprehensive textbook on reaction mechanisms, intended mainly for advanced students and postgraduates working on their PhD, and thus to render valuable service in the field of reaction mechanisms.

Part 1 explains the significance of symmetry and different types of bonds (90 pages), Part 2 methods for the elucidation of reaction mechanisms and reactive intermediates (90 pages), and Part 3 (heterolytic reactions) discusses aliphatic nucleophilic and electrophilic substitutions, the analogous reactions of aromatic compounds, and finally elimination and addition reactions (350 pages). The final Part 4 deals with homolytic and pericyclic reactions (120 pages). A subject index closes the book; there is no author index. Problems are given at the end of each chapter, but unfortunately without any indication of their solution. The printing of the reviewer's copy was not of the highest standard.

In view of the rapid development of the field of reaction mechanisms, it is doubtful whether a textbook of this kind could be satisfactorily written by a single author, for it is almost impossible for any single person to give a balanced and competent judgment in all parts of the field. In this book there are very diverse judgments, which incidentally do not correspond to the trend found in the primary literature. For example, the description of 1,3-dipolar cycloaddition (3 pages) hardly gets beyond the definition of the possible 1,3-dipoles. In the reviewer's opinion, however, the greatest shortcoming of this book is that the very numerous literature citations (and thus the arguments in the text) hardly ever reach 1974 and almost never go beyond it. For a "revised up-dated English version" of the Romanian edition of 1974 a more intense rewriting and supplementation would have been desirable.

Jürgen Sauer [NB 411 IE]

Vibrational Spectra of Organometallic Compounds. By *E. Maslowsky, Jr.*, John Wiley & Sons, Ltd., New York—London 1977. 1st Edit., xii, 528 pp., numerous figs. and tables, bound, £ 18.75.

Enormous advances have been made in organometallic chemistry in the last 25 years, and accordingly the number of important textbooks, monographs, and research reports is already legion. It is therefore all the more surprising that up to now there has been no collection and clear description of the IR and Raman spectroscopy of organometallic compounds. This is also surprising because IR and Raman spectra often provide the decisive proof for the structure of these compounds. This book is an attempt to close that gap. It is assumed that the reader is already familiar with the theoretical principles of vibrations and with problems of practical measurement. The results of other physical methods, such as X-ray structure analysis, NMR spectroscopy, and electron diffraction are always reported briefly if they are important for the interpretation of the vibrational spectra.

According to the Foreword, all compounds with direct metal-carbon interaction are considered, and the concept of a metal is thereby stretched very widely: it ranges from boron and silicon through the subgroup elements up to phosphorus. Purposely excluded, however, are the metal carbonyls and metal cyanides, unless other metal-carbon bonds exist there apart from M—CO or M—CN bonds. This limitation seems reasonable, since several reviews have been devoted to these compounds in recent years. However, it is not easy to see why metal-carbene and metal-carbyne complexes should not have been included.

The book is divided into three sections. Alkylmetal compounds are treated in the first section and compounds with unsaturated acyclic groups in the second. The third section is devoted to the metal derivatives of unsaturated cyclic organic ligands.

The internal arrangement of the book and presentation of the theme are very clear and easy to understand. Compounds of complicated structure are clarified by structural formulas. It is most welcome that the IR and Raman spectra of important complexes are not only described but also illustrated. The very many tables scattered throughout the text and the more than 2000 references (literature considered up to April 1976), together with the index—brief but very clearly set out—make the book equally suitable as a reference work. In this respect it is rather regrettable that there is no author index.

By and large the text has been carefully composed. A number of printing errors are distracting but do no appreciable harm. The book should, however, in no way be regarded as a mere collection of spectroscopic data. The author prevents this by occasionally mentioning controversies over the interpretation of the results or describing gradual approaches to the "truth" often extending over many years. Now and then too the limitations of the method are indicated. Thus, in spite of the rather inflexible material a book has arisen that reads easily for long stretches, and which will be of much value to the organometallic specialist, but can also be recommended to the general inorganic or organic chemist.

Helmut Fischer [NB 413 IE]

Elektrokinetische Grenzflächenvorgänge (Electrochemical Interfacial Processes). By *J. Weigl.* Verlag Chemie GmbH, Weinheim—New York, 1977. 1st edit., 196 pp., 98 figs., 10 tables, Reprotext, paperback, DM 36.00.

The electrokinetic or zeta potential plays an important role in colloid-chemical phenomena such as the stability or flocculation of dispersions. Since there is definitely a need for a handy book giving the fundamentals, the experimental methods, and some examples of applications, it is unfortunate that *Weigl*'s book fails to satisfy this need. In the fundamentals, the DLVO theory—the basis of the modern concept of colloid stability—is given only a very perfunctory treatment; it may perhaps be taken as an indication that the name *Deryagin* appears differently every time (but never correctly). It is difficult to see why, in a book published in 1977, the equations for the determination of the zeta potential from the electrophoretic mobility do not conform to SI units. The effect of non-potential-determining ions on the observed zeta potentials is mentioned only incidentally, without examples, and corrections for retardation and relaxation are not even mentioned. The description of the measurement methods is also very brief. Sources of error are not discussed. The book is best at the description of applications (mainly from the paper industry where the author's experience lies), and one can find here a few interesting connections between the zeta potential and other characteristics. Unfortunately, however, the author never mentions essential parameters involved in the determination of the zeta potential, such as the nature and charge of the gegenions and the ionic strength.

The book gives the impression that it was written in a hurry to meet a deadline, which may explain the stylistic shortcomings and the omission of some figure legends. Certain passages extending over pages are taken word for word from

other authors' publications (however, the author forgets the statement on page 46 that the text refers to TiO_2 and gives a misquotation on p. 165). In the references, the authors' initials are sometimes missing; reference 134 is Lehrbuch der Allgem. Chemie without the name of the author or the publisher.

"Reprotext" is the direct photomechanical reproduction of a typescript, and there can be no objection to it if it makes the book inexpensive. However, it calls for a correct typescript. In the present case, the bottoms of the letters often have not come out; one is also put off by the variations in spacing, the irregularities of the left-hand margin, and the consequences of not sticking the text together neatly, so that sometimes the lines are not even horizontal Blanks very often occur within words. It should have been the publishers' duty to eliminate such avoidable blemishes before printing. The back of the book broke after a single reading.

It is impossible to recommend this book.

H.-P. Boehm [NB 426 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Polymer Sequence Determination, Carbon-13 NMR Method. By *J. C. Randall.* Academic Press, London 1977. xi, 155 pp., bound, £ 11.70.—ISBN 0-12-578050-8

Akute Syndrome. Edited by *A. Anglhardt* and *H. Lommel.* Vol. 3 of the series "Methodische Fortschritte im medizinischen Laboratorium".—Verlag Chemie, Weinheim 1978. ix, 293 pp., bound, DM 62.—.—ISSN 0303-6278

Examens-Fragen Klinische Chemie. Edited by *K. Borner.* Springer-Verlag, Berlin 1977. vii, 175 pp., paperback, DM 18.—.—ISBN 3-540-08507-6

Atlas of Metal-Ligand Equilibria in Aqueous Solution. By *J. Kragten.* John Wiley & Sons, New York 1978. 781 pp., bound, *ca.* $ 47.50.—ISBN 0-470-99309-X

Grundlagen der Stoffübertragung. By *W. W. Kafarow.* Akademie-Verlag, Berlin 1977. xvii, 550 pp., bound, *ca.* DM 72.—

Survey of Progress in Chemistry, Vol. 8. Edited by *A. F. Scott.* Academic Press, New York 1977. xii, 284 pp., bound, $ 29.50.—ISBN 0-12-610508-1

Modern Aspects of Electrochemistry, No. 12. Edited by *J. O'M. Bockris* and *B. E. Conway.* Plenum Press, New York 1977. xii, 325 pp., bound, $ 39.00.—ISBN 0-306-37652-0

Catalysis in Organic Syntheses 1977. Edited by *G. V. Smith.* Academic Press, New York 1977. vii, 295 pp., bound, $ 15.00.—ISBN 0-12-650550-0

Collision Spectroscopy. Edited by *R. G. Cooks.* Plenum Press, New York 1978. xiv, 458 pp., bound, $ 54.60.—ISBN 0-306-31044-9

Polymer Science and Technology, Vol. 10. Polymer Alloys. Edited by *D. Klempner* and *K. C. Frisch.* Plenum Press, New York 1977. x, 491 pp., bound, $ 57.00.—ISBN 0-306-36410-7

Chemical Reaction Engineering—Houston. ACS Symposium Series 65. Edited by *V. W. Weekman, Jr.* and *D. Luss.* American Chemical Society, Washington 1978. xii, 619 pp., bound, $ 33.50.—ISBN 0-8412-0401-2

Verdampfen in Theorie und Praxis. By *Z. Rant.* Sauerländer Aarau, Frankfurt 1977. 2nd completely revised edition. xix, 425 pp., bound, *ca.* DM 120.—.—ISBN 3-7941-1516-3

Friction Materials. Recent Advances. By *L. B. Newman.* Noyes Data Corporation, Park Ridge 1978. x, 358 pp., bound, $ 36.00.—ISBN 0-8155-0688-0

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Transient Techniques in Electrochemistry. By *D. D. MacDonald.* Plenum Press, New York 1977. xii, 329 pp., bound, $ 45.00.—ISBN 0-306-31010-4

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A Coordination Chemist's View of Surface Science

By E. L. Muetterties[*]

Structure, a necessary element for an understanding of chemistry, has not been precisely defined, in molecular detail, for the surface species formed at a solid-gas interface. Dramatic advances in theory, instruments and experimental procedures have now provided the surface scientists with an impressive arsenal of structural and electronic probes. Chemistry in the form of the classic displacement reaction can also provide an insight to the structure of surface compounds. In fact, many of the experimental procedures and systematics of the coordination and organometallic chemist can be effectively utilized in a complementary fashion with surface physics techniques to gain a more definitive picture of chemisorption states and or reactions at a surface.

1. Introduction

A molecular understanding of chemical processes that occur at surfaces is essential to the advancement of science and technology in many diverse areas of surface science such as adhesion, corrosion, electrochemistry, catalysis and soil chemistry[1a]. Despite major theoretical and experimental advances during this century, especially in the last fifteen years[1b], the chemisorption process at a gas-solid interface remains a somewhat vaguely defined phenomenon in a structural context. Lack of a single definitive and general structural technique for the chemisorbed states has been and is still the major reason why a more precise molecular definition of chemisorption processes has not been realized. There are no precise analogs in the surface scientist's repertoire of physical techniques of the molecular chemist's three-dimensional X-ray analytical and nuclear magnetic resonance techniques, which so accurately and quickly limn the essential structural and stereochemical details of molecules. Advances in surface physics techniques have been especially impressive during the last decade notably in low energy electron diffraction[2] and angle resolved photoemission spectroscopy[3]. However, none of these techniques has the incisive and general applicability for full structural determination of the molecular chemists' three-dimensional X-ray analysis. Accordingly, surface scientists often must rely upon a complimentary set of data from many different physical measurements in order to infer the full molecular features of the chemisorbed state. Some of these techniques can be *relatively* simple in application and others presently require a dedicated experimental arrangement. Important among the former set are Auger spectroscopy[4], which can yield an elemental analysis of a surface, low energy electron diffraction[2] which can sense the ordering of metal atoms and of chemisorbed species at a surface, and mass spectrometry which samples the gas phase above the surface. An important new technique among the "dedicated" set is high resolution energy loss spectroscopy (HRELS)[5] which analyzes electrons inelastically scattered from a surface and which can provide vibrational information about chemisorbed species. A lexicon of common surface physics techniques is presented in Table 1.

Presently, a *structural interpretation at the molecular level* of data obtained from surface physics techniques is a nontrivial experimental and theoretical exercise. For example, low energy electron diffraction (LEED) data are difficult to interpret in precise and full structural detail at the molecular level. There are five distinct processes that must be considered in the

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Table 1. Lexicon of common surface physics techniques.

Technique	Principle	Application	Sensitivity (monolayer)	Penetration depth
Auger electron spectroscopy (AES)	Stimulated (typically electron stimulated) emission from valence or inner shell creates an excited ion. Auger electron is emitted in the deexcitation of the excited ion	Analysis of surface composition and electronic features	10^{-2}—10^{-3}	1—7 layers
Ion scattering spectroscopy (ISS)	Energy loss for rare gas ion scattering from a surface reveals the mass of the surface atom involved in the scattering process	Analysis of surface composition	$\approx 10^{-3}$—10^{-4}	1 layer
Secondary ion-mass spectroscopy (SIMS)	Ion (typically rare gas ion) stimulated secondary ion emission	Analysis of surface composition	$\approx 10^{-6}$	1 layer
Ion neutralization spectroscopy (INS)	Incident low-energy ions are neutralized by electron transfer from surface atoms which then stimulate an Auger electron emission	Analysis of surface composition and valence band structure	10^{-2}	1 or >1 layer
Electron spectroscopy for chemical analysis (ESCA)	X-ray stimulated electron emission from valence and inner shells of surface atoms	Analysis of surface composition and of surface atom oxidation states	$\approx 10^{-1}$—10^{-2}	1—7 layers
Ultraviolet photoelectron spectroscopy (UPS)	Ultraviolet radiation stimulated electron emission from valence shell of surface atoms	Electronic structure and orientation of chemisorbed molecules	10^{-1}—10^{-2}	1—3 layers ≈ 1 layer in synchroton radiation mode
Low energy electron diffraction (LEED)	Elastic scattering of low energy electrons from the surface and the near surface atoms	Symmetry features of surface atom environments, unit cell dimensions, and structural features of the surface	$\approx 10^{-1}$—10^{-2}	1—7 layers
High resolution electron loss spectroscopy (HRELS)	High resolution analysis of energy loss in inelastically scattered electrons from a surface	Analysis of vibrational states	10^{-2}	1—7 layers
Appearance potential spectroscopy (APS)	Programmed escalation of incident electron energy with scanning of the resultant X-rays from the surface	Analysis of surface composition and electronic features	10^{-2}—10^{-3}	1—7 layers

theoretical analysis[6] and a key consideration is the change in the potential function near the surface. Relatively definitive[7] structural interpretations of diffraction data have been achieved only for the case of chemisorbed atoms on a metal surface[8], and the only "molecular" chemisorptions to receive detailed analysis are those of acetylene on Pt(111)[9] and carbon monoxide on Ni(100)[10]. With recent experimental and theoretical advances[3], angle resolved photoemission spectroscopy can be employed to assess the orientation of chemisorbed molecules like CO, NO and CN on a "flat" metal crystal. Extensions to molecules of greater complexity are feasible but nevertheless more difficult. The low energy electron diffraction and angle resolved photoemission studies are complementary, with the former primarily sensitive when operated in the normal incidence mode[11] to distance parameters (distance between metal surface layer and the center of gravity of the chemisorbed molecule) and the latter very sensitive to the orientation of the chemisorbed molecule with respect to the metal surface plane. Both techniques have identified the same basic structures for sulfur atoms on Ni(100) (sulfur on four-fold sites within bonding interaction of four nickel atoms)[12, 13] and carbon monoxide on Ni(100) (carbon sitting atop individual nickel atoms)[10, 14]. Other techniques, now under study and development, should dramatically improve the arsenal of surface techniques, *e. g.* elipsometry for electronic and vibrational analysis, acoustical spectroscopy, surface sensitive (Auger-like electron) extended X-ray absorption fine structure, electron stimulated desorption, reflectance infrared and small angle neutron scattering.

Surface chemistry in its state of molecular development only ten or so years ago was rather analogous to the state of coordination chemistry at the turn of the century when no spectroscopic or diffraction techniques of structural significance were available. At that time, *Werner* in Germany[15] and *Chernyaev* in Russia[16], by utilizing chemistry that included displacement reactions, began to correctly infer stereochemical and structural features in coordination complexes. (This comparison is really invalid or at least unfair because the coordination complexes were susceptible to isolation and elemental analysis, and because resolution of enantiomers was feasible and was effectively utilized in the stereochemical studies.) There can be a similar utilization of the displacement reaction[17] in surface science, and, with the modern ultra-high vacuum chamber, the chemistry of individual single crystal metal faces can be explored. The displacement reaction, guided by analogy to established coordination chemistry, and of course supplemented with data derived from surface physics techniques could assist the advancement of the state of molecu-

lar structural knowledge of chemisorption processes. The potential of such a combined chemical and physical approach to surface science is described in this article. Analogy to coordination chemistry is utilized to structure the discussion and to incisively define critical regions where the analogy itself breaks down.

2. Terminology and Boundary Conditions

All the surface chemistry described below is referenced to a rather idealized world of surface science, a world far removed from the physical conditions that prevail under most practical surface science conditions. It is the world of ultra-high vacuum, $\approx 10^{-9}$ to 10^{-12} torr, the interface between a metal and a near vacuum. Experimentation in this area has been enabled by dramatic advances in vacuum technology[18]. There is a sound scientific basis for beginning with this idealized world. A pristine metal surface is a well defined starting state. The conditions which are essential to chemical studies of a clean metal surface can be realized only with the modern ultra-high vacuum chamber, and techniques, especially those based on electron diffraction and electron or photon spectroscopy, can be routinely applied to the chemisorbed state under these conditions. Although the extreme reactivity of a metal surface requires the clean ultra-high vacuum conditions, the chemistry of the surface can be explored under more conventional conditions. With a cell that may be lowered and raised so as to isolate the metal crystal from the vacuum chamber[19], it is feasible to effect chemical reactions, for example catalytic reactions, at the same metal surface under atmospheric or superatmospheric conditions and at virtually any temperature without major contamination of the main vacuum chamber and then later reexamine the metal crystal under high vacuum conditions by surface physics techniques[20]. The small area of the crystal face (about 0.5 cm^2) presents no problem today for the chemical studies because modern gas chromatographic and mass spectral techniques need only infinitesmally small amounts of material. The metal may be in virtually any physical form, a film, dispersed particles on a support, or a single crystal. Single crystals offer distinct advantages. A systematic investigation of the surface chemistry of the individual low Miller index faces as well as the high Miller index faces can identify the surface sites of low and high reactivity (see Fig. 1). It is also possible to selectively block different sites with foreign atoms as a further check of reactivity sites. The gap between ultra-high vacuum surface science and "real world" surface science can be and is being bridged today[21].

Chemisorption processes at metal surfaces typically are divided into two major groups: (i) associative processes in which there is no fragmentation of the molecule and (ii) dissociative processes in which bonds in the molecule are broken on chemisorption to give chemisorbed species that are molecular fragments. The paradigmatic dissociative process is that of chemisorption of hydrogen on transition metal surfaces to give hydrogen atoms which are bonded to metal atoms, *i.e.* to form metal-hydrogen bonds. The partitioning of chemisorption processes into associative and dissociative processes faithfully follows surface science terminology but the terms may convey to chemists a different and improper aspect of reaction mechanistic information. Unfortunately, the coordination chemist characteristically employs the terms dissociative and associative quite differently in a reaction mechanistic context[22].

For the individual classes of chemisorption, I shall employ as a partitioning scheme the types of reactions established in coordination and organometallic chemistry and will reference the discussion of surface chemistry to that of the coordination chemistry of zerovalent or low-valent transition metal chemistry.

3. The Surface Experiment

Since there will be extensive reference to the displacement reaction using metal single crystals in an ultra-high vacuum chamber, a brief description of equipment and procedure is presented here.

The single crystal of the desired orientation may be shaped[23] from a large crystal to the appropriate dimensions, *e.g.* a 5 mm diameter disk with a thickness[24] of about 1 mm and polished by a combination of mechanical, electrochemical and chemical procedures. The orientation is checked with the Laue X-ray diffraction pattern. If for example, the desired surface is a (111) face of a hexagonal close packed metal, the vast majority of the metal atoms will, in fact, reside in a pseudo-hexagonal environment after appropriate annealing of the crystal in the vacuum chamber. However, the surface is unquestionably heterogeneous. If viewed microscopically, the crystal will clearly display scratches and defects. Also there will be steps (see Fig. 1). The crystal will not be perfectly

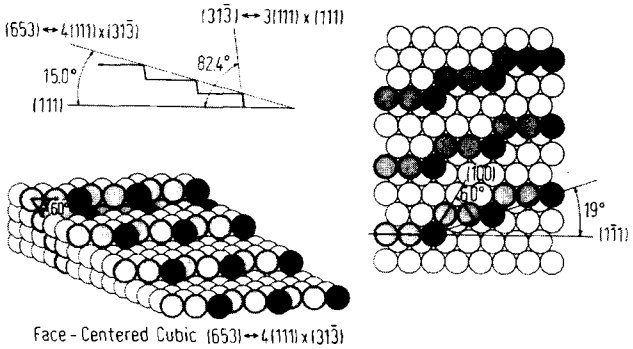


Fig. 1. A representation of a high Miller index plane for a face-centered cubic metal structure in which there are discrete areas described as: (i) "terraces", which are (111) sections with surface metal atoms (unshaded circles) that have a coordination number of nine, *i.e.* nine nearest neighbor metal atoms; (ii) "steps", where the metal atoms (light shading) have a coordination number of seven; and (iii) "kinks", where the atoms (dark shading) at the leading edge have a coordination number of six. (This drawing was prepared by Ms. *Carol E. Smith* at Berkeley.)

flat; a helium beam scattering experiment would show only 30—60 %[25] of the surface atoms to be in the same plane. However, these deviations from ideality do not appear to be severe limitations in the final analysis if there is a systematic chemical study of crystal faces. It is critical to underscore the point that many of the surface physics techniques that directly address the issue of structure focus primarily on the ordered structure and "ignore" the disordered structure—a point that surface scientists explicitly acknowledge but one that the casual reader of surface science literature may tend to either miss or forget.

After the orientation check by X-ray crystallography, the crystal is then welded either directly to metal support rods (the same or different metal) or to a metal (*e.g.* tantalum) backing to which is then welded tungsten wire and attached to insulated supporting rods[26]. The former arrangement provides a means of electrical resistance heating whereby all the current passes through the crystal and the latter an indirect heating arrangement with most of the electrical current passing through the metal backing[27]. Alternative mounting configurations have advantages in specific applications. A photograph of a mounted crystal is shown in Figure 2. The mounted crystal is then attached to the manipulator and inserted typically through the top port of the vacuum chamber (Fig. 3 and 4). The manipulator has rotational and translational degrees of freedom to allow for proper positioning of the crystal for individual experiments.

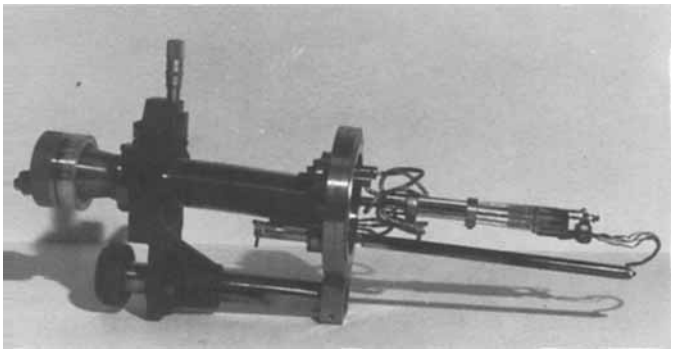


Fig. 2. Photograph of a metal single crystal mounted on a manipulator (from the laboratories of Prof. *Robert P. Merrill*). There are many possible variations in the mounting and peripheral features such as the heating element for the crystal. The arrangement illustrated here has a shielded cup that can be heated by an electron gun and thereby indirectly heat the crystal. Because the typical metal crystal has a very small volume, no significant thermal gradient across the crystal exists even at quite elevated temperatures. By modification, it is possible to cool the metal crystal to temperatures below 65 K. Temperature control and measurement can be quite precise. The depicted crystal manipulator effects controlled translational as well as meridianal and azimuthal rotational degrees of motion of the crystal. (This photograph was kindly provided by Mr. *Herbert Sawin*.)

After opening the chamber to emplace a crystal, an extended chamber reconditioning period is required. A bakeout at 500—550 K for a period of two days is typical. At this point, cleaning of the crystal can begin. The crystal is not only contaminated on the surface but also internally and these trace bulk impurities are potential surface contaminants. Very high initial bulk purities of six "nines" can lead to low surface purities if there is any tendency for segregation of impurities at the surface when the crystal is heated. The number of surface atoms in a metal crystal is about 10^{15} per cm^2 as compared to a bulk density of about 10^{22} atoms per cm^3. If there were 0.0001 % carbon impurity in the bulk and if there were a high degree of segregation at the surface, then the metal crystal could have a full monolayer of carbon on the surface after an annealing treatment. Thus, the metal crystal must be subjected to a stringent purification procedure.

Details of crystal cleaning procedures and the characterization of surface states often are not fully presented in the surface science literature[28]. Crystal cleaning procedures are recipes based on the crystal chemistry, the chemistry and the impurity segregation features peculiar to each metal. A

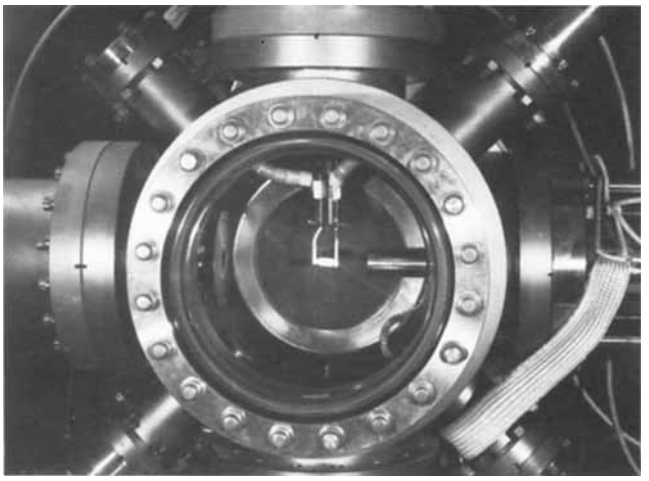


Fig. 3. A close-up photograph of an ultra-high vacuum chamber. In direct line of sight is the viewing port and within the chamber and in the center can be seen the metal crystal. Directly to the left of the crystal is the inlet to the mass spectrometer and to the right is an evaporating element for coating the metal surface by sublimation. To the 1:30 o'clock position is the glancing incidence Auger electron gun, the 4:30 position the leak valve connection and the 7:30 position the ion gun for ion sputtering experiments. To the rear is the low-energy electron diffraction screen and, hidden from view by the crystal, the electron diffraction gun which is at the center and to the rear of the screen. At the top and out of view is the crystal manipulator. (This photograph was kindly supplied by Prof. *G. A. Somorjai*.)

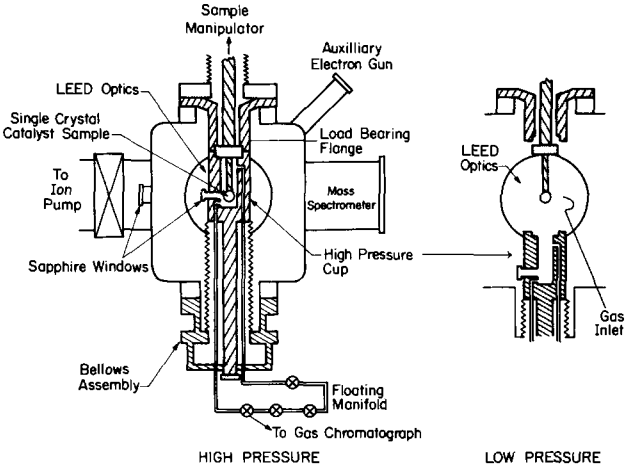


Fig. 4. A schematic drawing of a vacuum chamber, equipped with an isolation cell, and the peripheral equipment (courtesy of Prof. *G. A. Somorjai*). To the left is the schematic of the high pressure configuration and to the right the high vacuum configuration with the isolation cell lowered.

conventional cleaning procedure consists of ion (charged argon ion) sputtering of the surface at some temperature whose upper limit is set by phase transitions or the melting point of the metal and impurity segregation characteristics and whose lower limit is set by impurity atom mobility. For example, the major impurities in nickel are sulfur and carbon. Essentially all the sulfur and some of the carbon can be removed by argon ion bombardment at 1000 K. Because the carbon has a substantial bulk solubility at 1000 K, it is not quickly removed by sputtering at these temperatures. Surface segregation is however substantial at 680 K and this is the optimal temperature for carbon removal. Total cleaning time for nickel is about twelve to twenty-four hours and although minor traces of carbon may remain in the bulk, the surface will be essentially clean.

Surface purity is established by an Auger analysis[4] in which high energy electrons (1—5 keV) are directed at the metal crystal at grazing incidence angles or a normal incident angle (the conventional configuration of the low energy electron diffraction experiment)[29] (Fig. 5). The ejected electrons in this experiment have a relatively short mean escape depth, *ca.* 5—20 Å, so that the analysis is largely a surface elemental analysis. Figure 6 shows an Auger analysis of a carbon-doped nickel(111) surface. The Auger analysis for many elements can be very sensitive but is only semiquantitative (factor of two at best) as commonly applied[30].

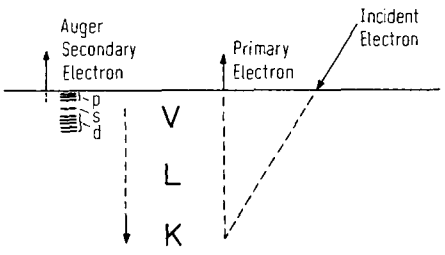


Fig. 5. A schematic representation of the Auger experiment. A beam of electrons or X-rays (1—5 keV) is directed at a surface. Electrons in the inner levels of an atom may be ejected if their binding energy is less than those of the incident beam. An electron vacancy created by this stimulation can be filled by a process in which an electron in a higher level drops into the vacancy. The energy released in this transition can be transferred to another electron (same or a different atom), which if its binding energy is less than the deexcitation energy transferred to it may be ejected into the vacuum. This secondary electron is the Auger electron and it has an energy characteristic that is a primary function of energy level separation in the ion. Thus an energy analysis of the emission electrons provides an elemental analysis of the surface. The emission escape depth of the Auger electron is a function of the energy and ranges from 1 to 7 atomic layers. The energy (energy shift) and the line shape (intensity *vs.* energy) can, in principle, provide electronic information about the environment of the atoms.

After a clean surface has been obtained and also defined by the Auger experiment, the surface must be annealed to correct surface irregularities that resulted from the crystal preparation and from ion bombardment[31] in the cleaning process. For nickel metal, an annealing at 1000 K for about one hour is usually sufficient as judged by the sharpness of the low energy electron diffraction spots and the lack of diffuse background in the diffraction pattern.

At this point, with a clean, oriented crystal face, the chemisorption experiment can begin; but before describing the chemisorption experiment a few comments about the vacuum and the critical pumping scheme would be in order. The vacuum chamber may be evacuated with a diffusion pump provided that efficient cold traps separate the pump and the chamber, otherwise hydrocarbon vapor would contaminate the vacuum system. A high-efficiency ion pump and a titanium sublimation pump are frequently employed, whereby vacuums in the 10^{-10} to 10^{-11} torr range can be attained. At 10^{-10} torr, the major gaseous species are usually H_2 and CO. Unfortunately, chemisorption of H_2 and CO are significant processes on metals like nickel at these pressures. Hence the metal surface will be "clean" at such fluxes for a period of about 60 minutes assuming a unitary sticking coefficient for the residual gaseous impurities. It is highly desirable to further reduce this background pressure because the lifetime of the "clean" surface would be raised and because the study of displacement reactions would be simplified. Reduction of H_2 and CO background to the nondetectable (mass spectrometric)

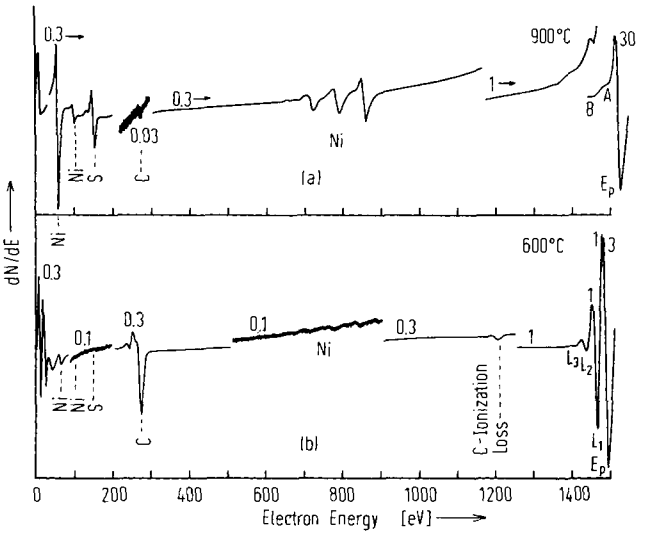


Fig. 6. Auger spectra from a nickel(111) surface, using a cylindrical mirror analyzer, which illustrates the phenomenon of impurity segregation in metals. The nickel specimen had been doped with carbon and there was a small sulfur impurity. a) This Auger spectrum is essentially that of a pure nickel surface at 900 °C, the carbon impurity atoms are largely in the bulk. b) At lower temperatures, 600 °C, there is a carbon segregation at the surface. The numbers 0.3, 0.03, *etc.* refer to sensitivity settings. The loss peaks L_1, L_2 and L_3 (plasma losses) are equally separated ($\approx$29 eV apart). (The spectra were kindly supplied by Prof. *J. Blakely* (cf. *H. R. Pati, J. M. Blakely*, J. Appl. Phys. *45*, 3806 (1974).)

level requires some type of cryogenic pump or a liquid nitrogen-cooled sublimation pump, which coupled in parallel with a turbomolecular pump is an excellent pumping arrangement in terms of speed and effective vacuum. A good turbomolecular pump can quickly reduce the pressure in a chamber to 10^{-9} torr, at which point the cryogenic pump can then preside to further reduce pressure to the 10^{-11} to 10^{-12} torr level. This pumping configuration although not common today may be so in several years.

In the chemisorption experiment, the reactant molecule is slowly introduced through a leak valve from a glass or metal manifold into the chamber through a hollow metal needle[32] directed at the crystal so as to minimize chamber contamination; alternatively an isolation cell may be employed to maximally limit chamber contamination. For less than a monolayer coverage of the metal crystal face, the exposure times required are a function of the flux of the molecule being introduced and the sticking coefficient for the molecule on the metal. With a near unity sticking coefficient, exposure times of 10—30 seconds are sufficient with quite low fluxes (10^{-9} to 10^{-10} torr pressure). This experiment is monitored with an ionization gauge and a mass spectrometer and optionally by the low energy electron diffraction pattern. The diffraction pattern has diagnostic value in that ordering of the chemisorbed layer usually will be evident immediately and, if not, the increase in background is a qualitative measure of the extent of coverage (Fig. 7). Care must be taken in electron scattering experiments to ascertain whether the electron beam itself may be affecting the structure of the chemisorbed species; the electron beam can damage the surface species. Auger electron spectroscopy provides the semiquantitative elemental analysis of the surface relative to the metal itself. At this point, a thermal desorption experiment, with the metal crystal face turned toward the inlet to the mass spectrometer, qualitatively measures the thermal reversibility

of the chemisorption process. In a reversible process, there is a regeneration of the clean metal surface and volatilization of the original molecule which can be so identified by its mass spectral pattern. If the thermal reactivity of the chemisorbed molecule is high relative to a molecular desorption process, the mass spectral analysis of gaseous desorption products will delineate the volatile decomposition products and an Auger analysis of the resultant surface will define the residual contaminant elements and their relative concentrations. The thermal desorption process[33-35] also can be assessed semiquantitatively so as to establish the heat of the desorption process and the order of the desorption process through a study of the desorption profile as a function of heating rate.

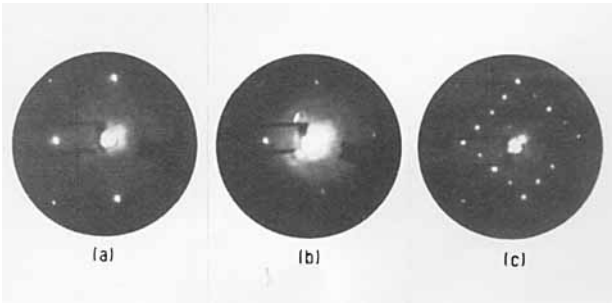


Fig. 7. a) A low energy electron diffraction pattern for a clean palladium(100) surface. The strong central spot is the zero level spot; three of the four first order spots can be clearly seen. b) Chemisorption of carbon monoxide at less than 0.5 monolayer yields a disordered chemisorption state on this palladium surface as shown by the much higher level of background in the pattern in the center; close inspection will reveal hazy higher order spots which demonstrate that there is some ordering of the carbon monoxide molecules under these conditions. c) Diffraction pattern for a half monolayer of CO on the Pd(100) surface. The pattern can be indexed as a centered (4×2) pattern rotated by 45°. This system was originally described by *J. C. Tracy* and *P. W. Palmberg*, J. Chem. Phys. *51*, 4852 (1969). (These photographs were kindly supplied by Dr. *S. D. Bader*, Argonne National Laboratory and Prof. *J. Blakely*, Cornell University.)

In a displacement reaction, the following is the ideal protocol: The molecule to be displaced and the displacing molecule should contain at least one element not common to the other so that the Auger analysis of the surface before and after attempted displacement has an incisive qualitative significance[36]. Ideally, the initial molecule should be chemisorbed on the metal surface with the metal crystal closed off from the major chamber by the isolation cell. With the metal crystal so isolated from the main chamber, the main chamber may be "lightly" preconditioned with the displacing molecule and then thoroughly evacuated. This procedure will maximize the possibility that the displaced molecule is generated from the metal crystal face rather than from the far reaches of the vacuum chamber. Then, the isolation cell may be removed and the introductory gas needle repositioned close to the metal surface. As the displacing gas is introduced through the needle, the system is monitored by mass spectrometry for detection of the original molecule if it is displaced. Finally, an Auger elemental analysis of the surface may be performed. In this manner, a semiquantitative analysis of the displacement reaction can be achieved. The displacement reaction may be effected at any temperature that is less than the temperature of molecular desorption or of some irreversible surface reaction. Because surface temperatures can be minimized in displacement reactions, this chemical probe should be a more general one than thermal desorption; the problem of thermal reactivity can also be minimized[36].

For the nonexpert, a measure of practical experimental time scales is noteworthy. The time required for a chemisorption experiment (after a clean surface has been achieved), the critically associated physical analyses (Auger and diffraction experiments) and a thermal desorption or chemical displacement reaction is about two hours. If, for example, a nickel(111) crystal is contaminated with carbon after these experiments, another 5—12 h of crystal purification procedure may be required. Practically speaking, the number of experiments per week per chamber is about three to seven for hydrocarbon-nickel(111) reactions. This number would be larger for iridium or tungsten which are easier to clean and substantially lower for iron which is extremely difficult to clean.

4. Classes of Chemisorption at a Metal Surface and a Chemical Approach to Characterization of these Classes

4.1. The Main Classes

Within the three main classes of chemisorption processes, associative, dissociative and polymerizative, there are many potential subclasses that are differentiated by reversibility, general structural features and molecular rearrangements[36]. All these classes and subclasses have their analogs in coordination chemistry[36]. I discuss first the three main classes of chemisorption reactions.

4.2. The Simple Associative Reaction Class

The conceptually simplest class of chemisorption processes is an associative and thermally reversible one in which the molecule is bound to one or several surface metal atoms with σ or σ-π bonds. For example, carbon monoxide chemisorbs on the (111) crystal face of platinum, and angle resolved photoemission data[37] for the platinum and nickel(111) cases are best interpreted in terms of a more or less perpendicular orientation of the CO molecule with respect to the surface with metal-carbon not metal-oxygen bonding—*i. e.* structural and stereochemical features that would be anticipated by analogy to coordination chemistry. It is not known whether the carbon atom is centered on a metal atom (terminal position) or between two or three metal atoms (bridging position); all three possible stereochemistries, the terminal and two bridging positions are known in molecular metal carbonyl clusters (see Fig. 8). Chemisorption of carbon monoxide on platinum or nickel is thermally reversible. On heating a nickel crystal (111 orientation) with chemisorbed CO, the desorption of CO has been detected by the sudden pressure increase, and confirmed by mass spectroscopic analysis, at *ca.* 440 K. The desorption process, a first order process, yields an *upper estimate* of the Ni—CO bonding energy of about 25—30 kcal/mol which is very close to the average Ni—CO bond energy in $Ni(CO)_4$[36].

To illustrate the potential of the chemical approach to surface science consider the specific example of acetonitrile chemisorption. Acetonitrile is a molecule characterized in transition metal coordination chemistry as a relatively weak ligand[38]; it is a weak σ donor and π acceptor. In contrast, CO, a weak σ donor but strong π acceptor ligand, is a relatively

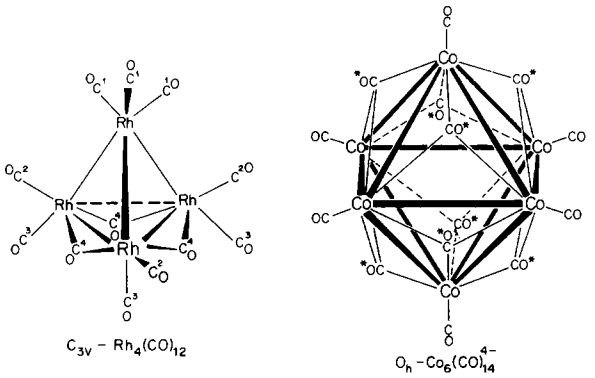


Fig. 8. Molecular geometry of the clusters $Rh_4(CO)_{12}$ and $Co_6(CO)_{14}^{4-}$, which, respectively, have idealized C_{3v} and O_h symmetry. In the former, there are four types of CO environments denoted by superscripts. One set comprises bridging carbonyl groups, superscript 4, which are C-bonded to two rhodium atoms. In $Co_6(CO)_{14}^{4-}$, there are six equivalent terminally bonded CO groups and eight triply bridging CO groups that are centered over the faces of the Co_6 octahedron. For crystallographic details see *C. H. Wei, G. R. Wilkes, L. F. Dahl*, J. Am. Chem. Soc. *89*, 4792 (1967); *V. G. Albano, P. L. Bellon, P. Chini, V. Scatturin*, J. Organomet. Chem. *16*, 461 (1969).

strong field ligand for zerovalent or low valent metal atoms. This characterization of CH_3CN and CO in coordination chemistry is nicely reflected in metal surface chemistry. For example, CH_3CN is weakly chemisorbed on the Ni(111) surface at 300 K and is reversibly desorbed at 360 K[36]. The estimated *upper* limit bond energy for the surface CH_3CN—Ni bond is 18—22 kcal/mol, a value substantially lower than that for carbon monoxide[36,39]. Most importantly, it has been shown that carbon monoxide easily displaces acetonitrile from the nickel surface, a process monitored by mass spectroscopy to show that the acetonitrile is actually displaced as the CH_3CN molecule. Auger analysis demonstrated that the resultant surface was free of nitrogen (CH_3CN) after the CO displacement reaction[36,39].

Another type of chemical experiment demonstrated that CH_3CN was not rearranged to CH_3NC in the chemisorbed state on nickel[39]. The isocyanide, CH_3NC, is a very strong field ligand in zerovalent or lower valent transition metal coordination chemistry and in molecular displacement chemistry; isocyanides generally displace CO readily from coordination complexes. As expected then by this analogy, CH_3NC was strongly chemisorbed on Ni(111) and could not be displaced by either CH_3CN or CO[39]. From this finding, it can be concluded that CH_3CN is not rearranged to CH_3NC, or *vice versa*, in these chemisorbed states. This chemical technique of utilizing structural isomers can be exceedingly valuable in establishing qualitative structural and stereochemical information about the chemisorbed state.

The structure of the chemisorbed state for CH_3CN on Ni(111) is not established. It is believed that the molecule is normal to the surface. Low energy electron diffraction studies show an ordered state; there is a (2×2) pattern which indicates that the unit cell of the ordered surface structure is twice that of the nickel surface structure and that in a rotational context the surface structure is aligned with the metal surface structure (Fig. 9)[37]. In principle, an analysis of the intensity

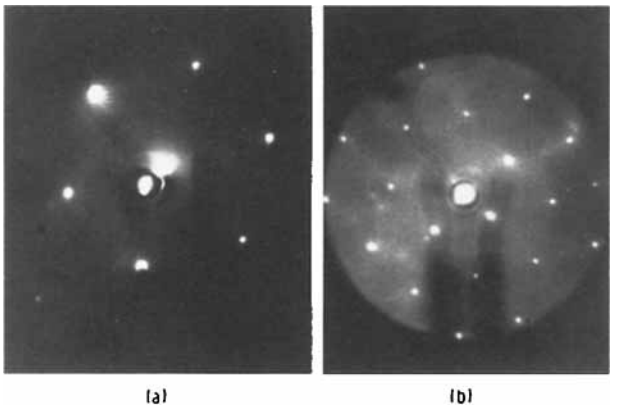


Fig. 9. a) Normal incidence low energy electron diffraction pattern for the face centered cubic nickel(111) crystal face. The large diffuse central spot is the zero order spot. In the ring of six spots, the real three-fold symmetry is qualitatively in evidence for these first order spots. b) (2×2) ordered pattern for CH_3CN on this nickel(111) surface taken at the same electron energy and a *nearly* identical perspective. All the first order nickel spots except two (to the right) can be seen and at half order positions are the additional spots that established the (2×2) pattern. The unit cell of the CH_3CN ordered structure is twice that of the nickel unit cell. The furrow patterns on the right are not fingerprints but are reproductions of the screen texture.

variation of the diffraction spots with change in incident electron energy could provide a structural characterization, but a definitive analysis would be very difficult. In point of fact, the size of the chemisorbed CH_3CN unit cell is a very important piece of information—it virtually requires that the molecule be normal to the surface; it cannot be linear and parallel to the surface. Considering the van der Waals' radii, it is not possible to place a perpendicularly oriented acetonitrile molecule above each nickel atom—but it is possible to place one molecule over every other nickel atom. This would then generate a (2×2) cell (also consistent with the diffraction data would be a displacement of the CH_3CN lattice so as to place the nitrile molecules in bridging positions; see Fig. 10).

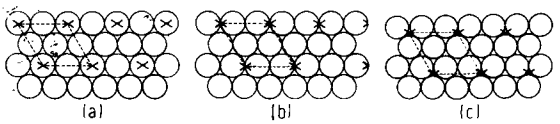


Fig. 10. Superimposed on the close-packed array of spheres representative of the (111) face of nickel are marks (X) that denote three of the symmetry limiting positions for CH_3CN molecules in the (2×2) chemisorbed state of CH_3CN (presumed to be normal to the surface). There is an infinite array of possible (2×2) structures because the only constraint here is a rotational correspondence between the lattices representative of the nickel atoms and of the chemisorbed acetonitrile molecules.

One might ask whether CH_3CN actually dissociatively chemisorbs—to give for example CH_3 and CN chemisorbed species. This specific possibility appears unlikely because it was demonstrated that the chemisorption of cyanogen $(CN)_2$ on nickel(111), where CN chemisorbed species are presumably

formed, is an irreversible process[39]. Cyanogen chemisorbed on a nickel(111) face is very strongly bound and thermally reacts above 770 K to evolve nitrogen gas[39].

An alternative and definitive chemical probe for detection of dissociative chemisorption processes is isotopic labeling. Thus, in the case of acetonitrile, chemisorption of a mixture of CD_3CN and $CH_3{}^{13}CN$ would not be expected to yield any $CD_3{}^{13}CN$ molecules on thermal desorption (a doubly labeled ^{13}CO—$C^{18}O$ experiment can be employed to detect reversible dissociative chemisorption of CO).

This limited and very simple study of CH_3CN and CO chemisorbed on nickel illustrates the potential of the displacement reaction for a characterization of the nondissociative, molecular class of chemisorption. A systematic study based on the displacement reaction should establish a ligand field strength series referenced to the various transition metals. It is anticipated that any nondissociatively or molecularly chemisorbed molecules should be subject to displacement by another molecule, if (i) their heats of chemisorption are not too disparate and (ii) the molecule is not rearranged or extensively rehybridized on chemisorption. In the first qualification, the constraints are not too severe because a thermodynamically unfavorable displacement reaction can be driven readily on a mass action basis in surface chemistry: the partial pressure of the displacing molecule can be varied over an enormous range, *e.g.* a pressure change by six orders of magnitude is a feasible change for an experiment. The second qualification relates to structural information and is nicely illustrated for the case of acetylenes and olefins.

Olefins or acetylenes bound to a single metal atom in a coordination complex are readily displaced by other molecules and the limited calorimetric data indicate that the metal-olefin bond energy is slightly less than the metal-carbon monoxide bond energy in a zerovalent transition metal complex[40]. Chemisorption of either acetylene or ethylene is not an especially exothermic process on copper and is probably endothermic on silver. The bonding of a molecule like ethylene on a copper surface may be a weak σ-π interaction analogous to the Dewar-Chatt-Duncanson model[41] (Fig. 11) of π bound

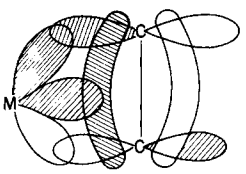


Fig. 11. Qualitative representation of the orbital interaction of the π and π* orbitals of an olefin with the acceptor and donor orbitals of a transition metal as originally presented by *Dewar* and by *Chatt* and *Duncanson* [41].

olefins in coordination complexes. The story for nickel metal is quite different. Acetylene, ethylene, propylene, and 2-butyne are all irreversibly chemisorbed on the nickel(111) face; attempted thermal desorption yielded only hydrogen desorption peaks at about 370 K[37]. Clearly these molecules are not simply bound in a σ-π fashion at single metal atoms at the surface of the metal. There remain two possibilities. These unsaturated molecules may be bound to two or more surface metal atoms by relatively strong σ metal-carbon bonds with an extensive rehybridization at the "unsaturated" carbon atoms of the acetylenic or olefinic molecule. Alternatively, these molecules may chemisorb with concomitant cleavage of C—H bonds to give molecular fragments that individually are no longer susceptible to a displacement reaction. Distinction between these two possibilities remains a major challenge in surface chemistry for it is directed to a very important general class of surface reactions.

It is desirable to effect displacement reactions at relatively low temperatures to avoid complicating side reactions derived from thermal reactivity of the chemisorbed molecule. Some displacements at a metal surface will proceed at room temperature and slightly below. Thus the activation energy for displacement can be as low as 15—20 kcal/mol. If the activation energy for chemisorbed molecules that contain C—H bonds were to exceed *ca.* 40 kcal/mol, the displacement reaction may not be effective because dehydrogenation, cleavage of carbon-hydrogen bonds, of the molecule will have an activation energy of this magnitude. These points raise interesting questions about the mechanistic details of the displacement reaction but there is no substantive information. For the time being, we may envisage a displacement reaction using a localized surface model. If a displacing molecule chemisorbs in a vacant site adjacent to the initially chemisorbed molecule there *may* be a weakening of the binding for the latter—chemisorption of another displacing molecule in another nearby site may then be sufficient for the displacement of the original molecule. For a flat metal crystal, associative[22] (bimolecular) displacement reactions at a single metal site are improbable simply because of geometric constraints.

4.3. The Simple Dissociative Reaction Class

Many diatomic molecules, X_2, chemisorb on transition metal surfaces with scission of the bond and the formation of M—X surface species. This dissociative type of chemisorption process is the invariant mode for hydrogen. Hydrogen chemisorption is reversible and the temperature required for the desorption of hydrogen as the hydrogen molecule is a function of the metal-hydrogen (surface) bond strength. For example, the desorption temperature (flash desorption maximum) is *ca.* 380 K for hydrogen on Ni(111)[39]. Hydrogen chemisorption is an oxidative addition reaction in that there is a small but net electron transfer from the metal to the hydrogen atom to form a "hydride-like"[42,43] ligand. A measure of the electron transfer in a chemisorption reaction can be obtained by a relatively simple electrical measurement in which the *change* in the work function is determined; this is the change in work function on chemisorption referenced to the clean surface. This experiment is an important adjunct to the other analyses of the chemisorption process although the derived information obtained in this fashion is qualitative in character.

Hydrogen chemisorption on a metal is analogous to the reversible oxidative addition of hydrogen to low valent transition metal complexes as in eq. (1), where there is a formal oxidation of rhodium from Rh(I) to Rh(III) with the formation of the two σ Rh—H bonds[44].

$$Rh^{I}Cl(PR_3)_3 + H_2 \rightleftharpoons H_2Rh^{III}Cl(PR_3)_2 \quad (1)$$

Analogous oxidative additions of halogens, oxygen, nitrogen and even carbon monoxide to some transition metal surfaces

are well established but generally these are irreversible, dissociative chemisorption processes. Among these diatomic molecules, an oxidative addition to a metal center in a coordination complex is known only for halogens [eq. (2)]. A dissociative

$$Ni^0(PR_3)_3 + Br_2 \rightarrow Ni^{II}(PR_3)_3Br_2 \quad (2)$$

addition of O_2, N_2, or CO probably would require a minimum of two metal atoms. Hence this type of process may be found only, if at all, for nitrogen and carbon monoxide in additions to dinuclear metal complexes or to metal clusters.

Cyanogen appears to behave like hydrogen; it oxidatively adds to the surfaces of nickel group metals, reversibly in the case of Pt(110) and irreversibly in the case of Ni(111) where N_2 is thermally desorbed at high temperatures leaving carbon on and in the nickel crystal. As a check of the parallel between this metal surface chemistry and coordination chemistry, we have found that thermal decomposition of $Ni(CN)_2$ yields N_2 and $(CN)_2$ whereas $Pt(CN)_2$ forms cyanogen[45]. Oxidative additions of cyanogen to metal centers in zerovalent and low-valent coordination complexes are well established [see *e.g.* eq. (3)[46]]. Thus, there is a qualitative parallel in the

$$(CN)_2 + Pt(PR_3)_3 \rightarrow (R_3P)_3Pt(CN)_2 \quad (3)$$

chemical behavior of these metal surfaces and their coordination complexes for this cyanogen chemistry. Nevertheless, a major differentiation between metal surfaces and zerovalent metal complexes is evident in their reactions with nitrogen, and, in some cases (some metal surfaces), with carbon monoxide. Complexation without fragmentation prevails in coordination chemistry and dissociative chemisorption in surface chemistry. It is this very differentiation that is the basis of the relatively facile hydrogenation of nitrogen or carbon monoxide by some metal surfaces, *e.g.* iron. Conceivably, a highly unsaturated metal cluster might be capable of dissociating nitrogen, but such a reaction is relatively improbable. The analogy between metal surfaces and coordination complexes or clusters will be invalid or inapplicable in some chemical areas; the area of CO and N_2 chemistry is one of these *for the more reactive metals like iron.*

Displacement of dissociatively chemisorbed molecules like hydrogen and halogens by another molecule requires a surface recombination of the "radicals". Displacement of hydrogen in surface M—H bonds or of halogen in surface M—Cl bonds into the gas phase as $H^{\bullet}$ or $Cl^{\bullet}$ or as H^- or Cl^- is clearly an improbable event. In a thermodynamic sense, the probability of displacement of dissociatively chemisorbed halogen or oxygen by some molecule is low for most metals but displacement of dissociatively chemisorbed hydrogen, as the hydrogen *molecule*, by another molecule is a different matter. Since the temperature required for thermal desorption of hydrogen is not very high for most transition metals—the maximum in the flash desorption of hydrogen from nickel(111) is *ca.* 380 K—, displacement of dissociatively chemisorbed hydrogen would seem to be a distinct possibility, and parenthetically an important finding, as will be discussed in Section 5.3. To date, our limited exploratory studies have been negative[39]. Exposure of a nickel crystal face(111), partially covered with hydrogen, to carbon monoxide did not seem to lead to desorption of hydrogen nor to a reduction in the flash desorption maximum for hydrogen. Perhaps the partially oxidized (through hydrogen oxidative addition) nickel surface so reduces the CO heat of chemisorption that a substantial weakening of the Ni—H bond is not feasible[39]. A stronger acceptor molecule then seems to be required. Donor molecules should increase the strength of the Ni—H bond *if* in this sector the analogy to coordination chemistry is reasonably valid. Alternatively, the displacing molecule could be selected among the diatomic molecules that strongly and dissociatively chemisorb. Cyanogen, a *quasi* diatomic or halogen-like molecule in that the C—C bond is weak and readily broken, could be an excellent molecule for hydrogen displacement from a surface. Iodine is a reasonable alternative to cyanogen but not a very practical one because of substantial contamination problems[47]. In some of these interactions, there may be a chemical reaction rather than a simple displacement so as to yield HX rather than H_2—in such a variation, the diagnostic value would be retained.

4.4. The Polymerizative Chemisorption Class

The antithesis of dissociative chemisorption is a molecular chemisorption whereby there is polymerization or oligomerization of many or several of the molecules. A possible example is the trimerization of acetylene to benzene. Because this type of chemisorption is not a first order process it is an unlikely event unless there is a high mobility of the molecules on the surface so that two or more molecules can approach and orient in such a fashion as to allow oligomerization to proceed. Polymerization initially at or on the surface and then out away from the surface (not totally on the surface) is however a well-established phenomenon in surface chemistry[48].

Chemisorption of cyanogen on nickel(111) at 300 K does not give an ordered chemisorbed layer[39]. However, warming to 400 K gives a very stable ordered (6×6) structure (see Fig. 12)[39]. Because the C—C bond energy in cyanogen, NC—CN, is low and because CN is a strong field ligand in metal coordination chemistry, initial dissociative chemisorption is a highly probable event. Now CN could be normal or parallel to the metal surface. In binary low-valent transition metal cyanides, the cyanide ion is bonded to two metal ions in

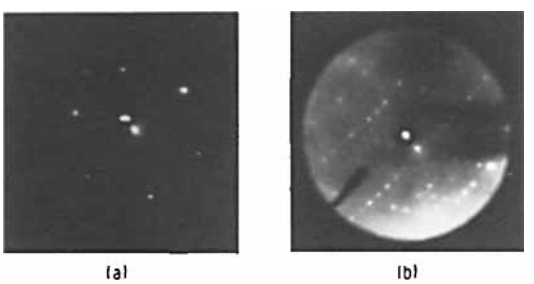
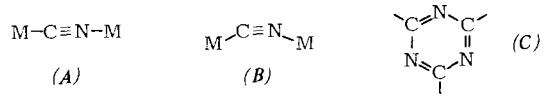


Fig. 12. a) Low energy electron diffraction pattern for a clean (111) face of nickel; b) (6×6) ordered pattern of cyanogen chemisorbed on this nickel face. The centered light spot with a dark halo is from the electron gun itself.



(A) (B) (C)

a linear array (*A*). This geometry is not feasible on a flat (111) metal face but a bent array (*B*) is feasible and plausible. If a parallel orientation prevails for CN on Ni(111), mobility of the CN species on the surface could allow for a polymerization of the CN species to give a bound triazine derivative with the skeletal array (*C*). Two of these units could neatly fit into a (6×6) unit cell or to give a net similar to the layer nets observed in nickel group cyanides, *e.g.* $Ni(CN)_2$.

Polymerization of unsaturated organic molecules on coordination to a low-valent metal atom is established in coordination and organometallic chemistry. Trimerization of acetylenes to benzenes is a relatively common reaction and the trimerization of butadiene to 1,5,9-cyclododecatriene[49] is known for zerovalent mononuclear nickel complexes.

5. Subclasses of Chemisorption on a Metal Surface

5.1. Subclasses of Associative Chemisorption: Extensive Rehybridization within the Molecule

Chemisorption of molecules that contain multiple bonds may involve an extensive rehybridization at the multiply bonded atoms. This possible type of chemisorption is appropriately considered with respect to the coordination chemistry for an acetylene molecule, RC≡CR. The simplest form of an acetylene chemisorption would be a σ-donor interaction of a π acetylene orbital and π-acceptor interaction of a π* acetylene orbital with surface metal atom orbitals[50]. This would be fully analogous to the Dewar-Chatt-Duncanson[41] model of the ethylene-metal interaction (Fig. 11), and by analogy would yield a relatively weakly bound molecule which should be susceptible to facile displacement by other molecules such as carbon monoxide. However, acetylene compounds such as acetylene itself and 2-butyne, are very strongly bound on nickel(111)[39], as an example of one well studied metal surface, and are not displaceable from the nickel surface by other molecules[39].

There is an alternative binding of an acetylene if there are two or more adjacent metal atoms. Significant rehybridization of the acetylene carbon atoms may allow σ carbon-metal bonds, minimally two in number per acetylene carbon atom,

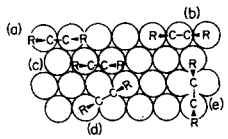
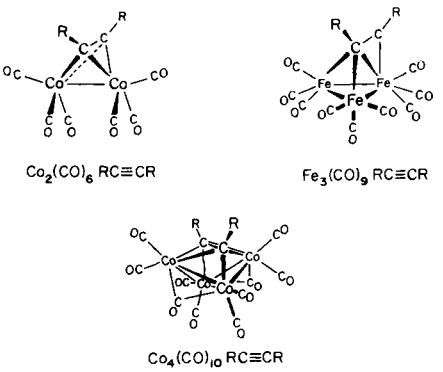


Fig. 13. Possible orientations (a—e) of a molecule RC≡CR on a close-packed metal surface ((111) face). All orientations other than the one centered on a single metal atom yield two or more metal-carbon bonds to the acetylenic carbon atoms.

to be formed (Fig. 13)[51]. This type of acetylene binding is well documented in coordination chemistry for metal dinuclear and cluster complexes (Fig. 14)[51,52]. Rather extensive studies of these polynuclear metal acetylene complexes have demonstrated a robust acetylene binding. Acetylene exchange reactions in these polynuclear complexes does not occur readily whereas such exchange reactions are facile in mononuclear metal acetylene complexes (Fig. 11)[52]. For example, diphenylacetylene exchange with di-*p*-tolylacetylene is extremely slow in the nickel-acetylene cluster complex, $Ni_4[CNC(CH_3)_3]_4(C_6H_5C{\equiv}CC_6H_5)_3$ at 300 K (reaction times of days). In the case of $[C_5H_5Mo(CO)_2]_2C_2H_2$ the exchange is detectable only at temperatures above 370 K[52].



$Co_2(CO)_6\,RC{\equiv}CR$ $Fe_3(CO)_9\,RC{\equiv}CR$

$Co_4(CO)_{10}\,RC{\equiv}CR$

Fig. 14. Molecular structure of three classes of polynuclear metal-acetylene complexes (see discussions in references [51] and [52]). The bond length $d_{C\equiv C}$ in $Co_2(CO)_6RC{\equiv}CR$ is 1.35 Å, in $Fe_3(CO)_9RC{\equiv}CR$ 1.41 Å, and in $Co_4(CO)_{10}RC{\equiv}CR$ 1.44 Å (mean values).

If the surface-coordination chemistry analogy is valid, an unsaturated molecule bound to a metal-surface through extensive σ-bonding of adjacent metal atoms to the (initially) unsaturated atoms, will not be subject to facile displacement by another molecule, at least at 300 K. The activation energy may be high for such displacements; in some cases, the activation energy may be greater than for alternative thermal reactions of the chemisorbed molecule. Possibly the displacement may be more readily effected with a molecule whose dissociative chemisorption raises the level of surface oxidation and decreases the binding energy of the initially bound molecule.

5.2. Subclasses of Associative Chemisorption: Molecular Rearrangement

A molecule may chemisorb on a metal surface without fragmentation (dissociation), but through a rearrangement of bonds within the molecule it may yield a chemisorbed species topologically disjoint from the original molecule. For example, an allene $R_2C{=}C{=}CR_2$ molecule may on chemisorption yield an acetylenic bound species ($R_3CC{\equiv}CR$). This possibility can be accurately probed by examining the chemisorption process for the individual isomers. We have exploited this chemical probe so as to demonstrate that CH_3CN and CH_3NC chemisorb as chemically and physically distinguishable isomers on the (111) face of platinum and nickel[39].

All isomerization-based chemisorption processes are definable by a study of isomeric molecules and, if necessary, by isotopic labeling for an ultimate characterization by mass spectroscopic analysis of gaseous desorption products from a displacement reaction.

5.3. Subclass of Dissociative Chemisorption: Molecular Fragmentation in Hydrocarbons

The chemical feature that sharply distinguishes metal surface chemistry from known coordination chemistry, either that of mononuclear or polynuclear complexes, is the ease with which carbon-hydrogen bonds in organic molecules can be cleaved. Dehydrogenation of organic molecules is a thermodynamically and kinetically favorable process for clean metal surfaces, particularly under conditions whereby these reactions are effected in ultra-high vacuum chambers. This type of reaction is incisively documented for the chemisorption of ethylene on tungsten, where dehydrogenation occurs below 300 K to yield chemisorbed acetylene (or an isomer) and then C_2 (carbon) chemisorbed species are formed as the temperature is raised above 300 K[53].

This potentially complex pattern of hydrocarbon chemisorption on a metal surface is of fundamental significance, especially in heterogeneous catalysis. For example, ethylene might chemisorb at 25 °C to give (i) a molecular ethylene complex, (ii) vinyl ($CH{=}CH_2$) and hydride metal surface species, (iii) an acetylene and two hydride metal surface species, or (iv) a carbene or quasiallene species (CCH_2) and two metal hydride surface species. An example of the last possibility established in metal cluster chemistry is illustrated in Figure 15[54].

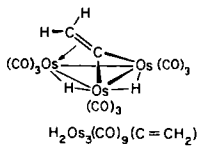


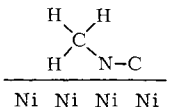
Fig. 15. Molecular structure of the cluster reaction product of ethylene and $H_2Os_3(CO)_{10}$ [54].

Actually, dissociative chemisorption of ethylene on metal surfaces is a relatively common surface phenomenon but the nature of the resultant chemisorbed hydrocarbon is not known.

Only one physical technique is available that will distinguish definitively between a molecular or an associative chemisorption and a dissociative chemisorption in which a molecular fragment or new molecule is generated by one or more carbon-hydrogen bond scissions per molecule. This technique, high resolution energy loss spectroscopy[5], can discern the energy loss in inelastically scattered electrons associated with metal hydrogen bond vibrational excitations. At present this is not a routine technique and cannot be used with facility in general chemical studies of the chemisorbed state. Nevertheless, the four to six instruments, extant or under construction, could answer a number of key scientific questions in metal surface-hydrocarbon chemistry.

If M—H surface species could be displaced as hydrogen gas by a second molecule, then surface science would have a facile diagnostic chemical technique of tremendous general import. One practical problem in accurately assessing hydrogen desorption through a displacement reaction is that when a molecule with any capacity to chemisorb on metals is introduced into the chamber there will be a momentary increase in the hydrogen background—typically, most of this is not associated with desorption from the single crystal of metal but rather from chamber walls or a bit of ion pump indigestion which literally throws hydrogen gas back into the chamber. An isolation cell and cryogenic pumping can minimize this problem; the elegant solution is a molecular beam displacement experiment. Development of such a diagnostic chemical probe is a major objective of our research.

Methyl isocyanide is strongly chemisorbed on the (111) face of nickel[39]. Initial chemisorption probably involves a bonding interaction of the carbon and nitrogen atoms of the isocyanide with several nickel atoms; there is a precedent for such a bonding interaction in a nickel isocyanide cluster molecule, $Ni_4[CNC(CH_3)_3]_7$[55]. In this case, the C—N axis would be above and more or less parallel to the nickel surface as in (*D*) and this then places the hydrogen atoms of the



(*D*)

methyl group proximal to the surface. In coordination chemistry, the close approach of a ligand hydrogen atom to a coordinately unsaturated metal atom can lead to an oxidative addition of the C—H bond[56, 57]. Hence, oxidative addition of a C—H bond to a proximal nickel atom in the methyl isocyanide case should be a relatively favorable process.

CH_3NC is irreversibly chemisorbed on nickel and is not susceptible to displacement by other molecules. With flash heating, hydrogen is desorbed at several temperatures, the lowest of which is 380 K, the characteristic desorption temperature for hydrogen[39]. If the crystal with chemisorbed CH_3NC is annealed at *ca.* 350 K before flash heating, no hydrogen is desorbed at 380 K, though hydrogen desorption does occur at elevated temperatures[39]. These thermal desorption experiments suggest that CH_3NC on chemisorption undergoes a further reaction, a dehydrogenation, either at 300 K or slightly above. Dehydrogenation reactions of ligands are not as common in coordination chemistry as on metal surfaces but they are well documented for low valent and coordinately unsaturated complexes in which a ligand hydrogen atom is in close proximity to the metal atom[56, 57]. Several examples are illustrated in Figure 16.

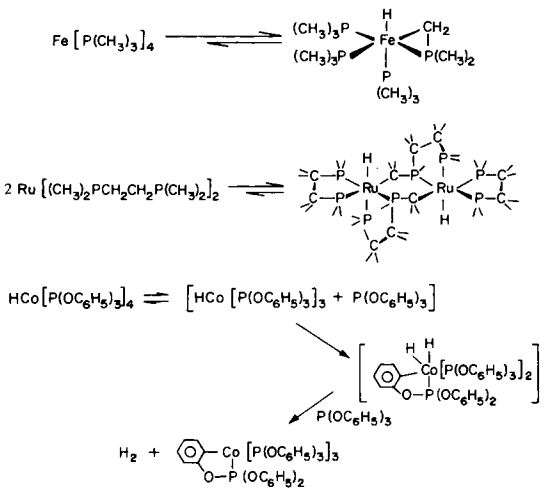


Fig. 16. Examples of molecular metal complexes in which an intramolecular C—H bond addition across the metal center has occurred to yield a metal-carbon and a metal-hydrogen bond. (For a more complete discussion, see the reviews by *Parshall* [56] and by *Webster* [57].)

Any chemisorption of an unsaturated hydrocarbon or hydrocarbon derivative that places carbon-hydrogen bonds close to surface metal atoms is apt to be accompanied by a cleavage of these carbon-hydrogen bonds. In the acetonitrile chemisorption on nickel, the perpendicular alignment of the nitrile places the carbon-hydrogen bonds of the methyl group sufficiently distant from the surface nickel atoms that C—H bond scission does not substantially occur on chemisorption at 300 K. On the other hand, olefins and acetylene should chemisorb initially with the unsaturated carbon-carbon bond more or less parallel to the metal surface thereby orienting substituent atoms near the metal surface. In these cases, carbon-hydrogen bond cleavage is a probable process near or slightly above room temperature at least for the more active metals. Aromatic hydrocarbons should exhibit a similar behavior. Low energy electron diffraction data for benzene chemisorbed on platinum are available but an intensity analysis has not been made[58]. The unit cell size is such that several models would appear to be possible. One possible model has a bound dehydrobenzene molecule formed by a dehydrogenation reaction. This dehydrobenzene species could be bound to the platinum surface through two σ Pt—C bonds and then, by tilting of the ring away from the normal, further bound through a π bond with additional surface metal orbitals. Interestingly, there is a model for this suggested chemisorbed state of benzene in molecular metal cluster chemistry. Benzene reacts with $Os_3(CO)_{12}$ at *ca.* 473 K to form a dehydrobenzene complex which presumably[59] has the structure shown in Figure 17.

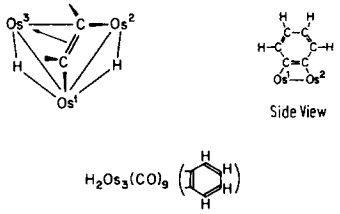


Fig. 17. Structure postulated for the reaction product from $Os_3(CO)_{12}$, or better $H_2Os_3(CO)_{10}$, and benzene [59]. An X-ray crystallographic study is required for confirmation of this postulate. A precise determination of C—C bond separations in the six-membered ring may provide a better indication of the nature of the bonding between the ring carbon atoms and the unique osmium atom.

One intriguing chemical possibility for modification of a dissociative (C—H bond scission) chemisorption of an olefin, an acetylene, or an aromatic hydrocarbon would be to presaturate the surface with hydrogen before chemisorption of the hydrocarbon—this might inhibit or even totally block carbon-hydrogen bond scission in the bound hydrocarbon.

6. A Model for Hydrogen Atom Mobility in Hydrocarbons

A general feature of surface chemistry is the hydrogen atom lability in hydrocarbon species chemisorbed on metal surfaces; H—D exchange is generally a facile process in C_xH_y—C_xD_y or C_xH_y—D_2 mixtures. Recently, *Shapley et al.*[60] showed that a methyl derivative of an osmium cluster is in a facile equilibrium with a methylene-hydride cluster derivative (Fig. 18). This discovery in metal cluster chemistry provides a possible model for the nearly pervasive phenomenon of hydrogen atom lability in chemisorbed hydrocarbon species.

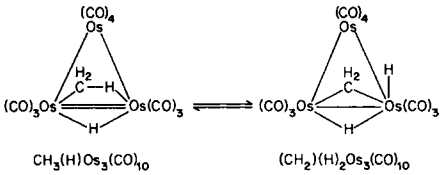


Fig. 18. The structures [60] of the equilibrium solution species of composition $Os_3(CO)_{10}CH_4$ [60]. The methylene structure has been defined by an X-ray crystallographic analysis of a single crystal of this isomer. Although the precise structure of the methyl derivative is yet to be defined for the crystalline state, the spectroscopic data suggest that the methyl group is in an unsymmetric bridging position.

7. Orientational Effects

The obvious critique of the high vacuum, single crystal surface technique is that a single crystal face hardly emulates a metal film or highly dispersed metal particles. The point is granted. However, a careful assay of the chemistry of a given metal requires a systematic investigation of the key crystal face chemistry for the metal in question. Crystal face chemistry can be demonstrably diverse. For example, the platinum (110) surface reversibly chemisorbs cyanogen in a relatively strong fashion yet the (111) face of platinum reversibly interacts with cyanogen to a very minor extent. Thus, the details of single crystal metal chemistry can delineate, in principle, the essential bonding or geometric details of the chemisorption process. *Somorjai et al.*[19] have demonstrated the difference in reactivity of surface metal atoms that lie in different environments, *e.g.* the atoms in the terraces, steps and kinks of high Miller index faces which come closer to real surfaces than do low index or "flat" crystal faces.

The metal-metal coordination number for individual surface metal atoms is markedly affected by the nature of the crystal face. In the terrace or flat section of a (111) face of a face-centered cubic metal, the coordination number is nine—if there is a break, a step, in this terrace, the metal atom at the top of the riser has a coordination number of seven—if the step is irregular so as to generate a kink, the leading atom of a kink has a coordination number of six (Fig. 1). Adatoms on a terrace have coordination numbers of three, four and five for a single, a pair and a triad of adatoms, respectively.

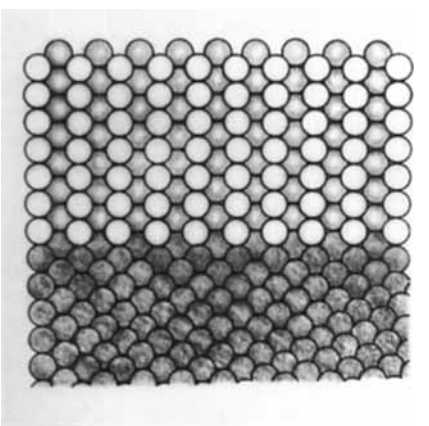


Fig. 19. A representation of the (110) face-centered cubic structure. The representation is generated from the (111) face (dark shaded lower region) and clearly shows the ordered step-like character of this low Miller index face, a face of relatively low thermodynamic stability which often undergoes reconstruction under the conditions of a chemisorption process.

A (110) face of a face-centered cubic metal is like a stepped surface (Fig. 19 and 20) and the "protruding" atoms have a coordination number of only seven. We would expect to a first approximation that site reactivity of surface metal atoms

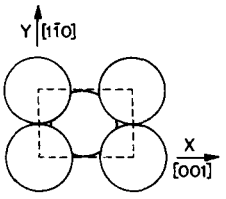


Fig. 20. The unit cell for the (110) face of a face-centered cubic crystal. Coordination number for the top four atoms is only seven whereas it increases to eleven for the partially covered central metal atom.

will rise sharply with the decrease in the metal-metal coordination chemistry as observed for molecular coordination compounds. The initial studies of *Somorjai* are consistent with this speculation; it will be of great importance to test this hypothesis in general systematic chemical studies of metal crystal face chemistry.

I wish to sincerely thank the Chemistry Faculty and the Hitchcock Foundation of the University of California at Berkeley for their hospitality and support during my stay in Berkeley in the spring of 1977. The research was generously supported by the Department of Energy. I am especially indebted to Professor Gabor Somorjai and Dr. John C. Hemminger for an introduction to surface science. Much of the preliminary research (cited in this article) based on a chemical approach to surface science resulted from collaborative research with Drs. Somorjai and Hemminger.

I also wish to acknowledge the detailed and constructive comments of my Cornell colleagues, particularly Professors John Blakely, Thor Rhodin and Robert Merrill and the support of my research in coordination chemistry by the National Science Foundation and the Cornell Materials Science Center.

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[6] According to *Tong* [2] these are (i) energy dependent electron scattering cross sections from surface atoms, (ii) inter- and intraplanar multiple scattering of electrons from surface atoms, (iii) inelastic damping of the incident flux by surface plasmon and single particle excitations, (iv) electron-phonon scattering contributing to an effective Debye-Waller factor, and (v) diffraction of electrons at the potential discontinuity at the vacuum-solid interface.

[7] In the final analysis, there is a visual comparison of the experimental curve with the theoretical curves for postulated models. If carried out systematically, this analysis gives a complete picture for *atoms* chemisorbed on the surface. Comprehensive analysis of the chemisorption state of a *molecule* on a surface is at best difficult because a molecule may chemisorb, with the topological or graphical features of the molecule intact, with rearrangement, with polymerization, or with scission of one or more bonds. As was true in the early days of electron diffraction of gaseous molecules, chemical intuition is a most important element in the study of molecules chemisorbed on surfaces.

[8] A comprehensive enumeration of low energy electron diffraction studies has been presented by *Tong* [2]. The especially notable studies of atoms chemisorbed on a metal surface initiated by *T. N. Rhodin et al.* (Cornell University) and by *S. Andersson et al.* (Chalmers Institute of Technology) set the stage for the theoretical development of the analysis by *Duke, Pendry, Jepsen* and *Marcus*. See the application by *J. E. Demuth, D. W. Jepsen* and *P. M. Marcus*, Phys. Rev. Lett. *31*, 540 (1973) and *32*, 1182 (1974) for the overlayer structures of O, S, Se and Te atoms on Ni(100), Ni(111) and Ni(110).

[9] *L. L. Kesmodel, P. C. Stair, R. C. Baetzold, G. A. Somorjai*, Phys. Rev. Lett. *36*, 1316 (1976).

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[12] *J. E. Demuth, D. W. Jepson, P. M. Marcus*, Phys. Rev. Lett. *31*, 540 (1973).

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[15] See introduction by *J. C. Bailar* in *A. E. Martell:* Coordination Chemistry. Van Nostrand Reinhold, New York 1971, Vol. 1, p. ix.

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[17] One of the earlier utilizations of this technique in surface science was by *K. H. Maxwell* and *M. Green* for germanium surfaces. J. Phys. Chem. Solids *14*, 94 (1960).

[18] Not too many years ago, attainment of 10^{-10} torr vacuum was the basis for doctoral physics dissertations but the realm of 10^{-10} to 10^{-12} torr vacuum is now routinely accessible.

[19] *G. A. Somorjai*, Acc. Chem. Res. *9*, 248 (1976).

[20] The alternative is a molecular beam reaction with differential pumping. Although this alternative can present high flux densities to the metal surface, momentum transfer conditions may complicate the interpretation of data.

[21] In some instances, there is no significant kinetic or thermodynamic differentiation between the high vacuum and the atmospheric or super atmospheric reactions, as in the $CO+O_2$ reaction (*D. R. Monroe*, Ph. D. Thesis, University of California, Berkeley 1972). For other reactions, the thermodynamic parameters change markedly with pressure. Most critically, a pure metal surface is often not representative of the so-called metal catalysts where oxide phases and carbon overlayers are often the dominant surface phases.

[22] In surface science, the terms associative or dissociative refer explicitly to chemisorption processes of molecules that occur, respectively, with no fragmentation or with fragmentation of the molecule. In coordination chemistry, the term dissociative or associative reaction has a reaction mechanistic connotation. A dissociative reaction follows a step sequence

$$ML_x \rightleftharpoons ML_{x-1} + L \quad \text{and} \quad L' + ML_{x-1} \rightleftharpoons ML_{x-1}L'$$

whereas associative follows the sequence

$$ML_x + L' \rightleftharpoons ML_xL' \quad \text{and} \quad ML_xL' \rightleftharpoons ML_{x-1}L' + L$$

(See *C. H. Langford, H. B. Gray:* Ligand Substitution Reactions. Benjamin, New York 1966, Chap. 1.) Since reactions of molecules with a metal surface will almost invariably be associative in a reaction mechanistic context, the less compact terminology of molecular associative and molecular dissociative chemisorption is now recommended to avoid any confusion by scientists from different disciplines. New chemisorption terminology such as fragmented and intact, although more concise, might be less readily accepted by the surface science community because the present terms are of long standing usage.

[23] The desired crystal may be cut from a larger crystal by an electric arc or a diamond saw or alternatively may be purchased to specification.

[24] Diameter and thickness will vary substantially in practice depending upon the nature of the physical and chemical studies.

[25] With care, this percentage figure can be raised to 80—90%.

[26] This is not a standard or preferred mounting procedure but merely an example.
[27] The metal sample may also be heated indirectly by electron bombardment of a shielded metal cup as shown in Figure 2.
[28] Full characterization details for surface states are critical elements in scientific publications. Cleaning procedures should also be presented for further insight into the research and for assistance to others not familiar with the particular metal in question.
[29] The grazing incidence experiment has the advantage of greater sensitivity. With the cylindrical mirror analyzer which is of the window filter type, a maximal signal-to-noise ratio can be realized. With a cylindrical mirror analyzer, the Auger analysis can be achieved in a very short time, 10^{-2} seconds, compared to times of about one minute for the retarding grid analyzer—thus, potential electron beam damage to the surface species can be minimized. This method of Auger electron analysis is the method of choice if line shape information is desired.
[30] A careful analysis of standards can raise the level of the Augur analysis to a substantial degree. In addition, the line shape of the Auger peaks can, in principle, provide details of the structural and electronic states of the chemisorbed states. Careful comparative studies of the isolated gas phase spectra of molecules with their spectra on chemisorption on surfaces may provide information about intimate features of the chemisorbed states; see *J. M. White, R. R. Rye, J. E. Houston*, Chem. Phys. Lett. *46*, 146 (1977).
[31] Ion bombardment actually results in some rare gas ion implantation in or near the metal surface. The implanted ions are removed on annealing the metal.
[32] The needle method of introduction or the alternative sintered glass channel plate present problems for uniform introduction of gas molecules to the metal surface. A more uniform flux presentation to the surface can be achieved with an effusive molecular beam.
[33] Thermal desorption studies, despite their conceptual simplicity, require experimental sophistication if quantitative details are to be derived [34, 35].
[34] *T. N. Rhodin, D. L. Adams* in *N. B. Hannay:* Treatise on Solid State Chemistry. Plenum Press, New York 1976, Vol. 6A, p. 343.
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[42] The issue of the electronic character of the transition metal-hydrogen bond is still open to interpretation. It is a covalent—not an ionic bond. Polarity of the bond would appear to be best [43] represented as $M^{\delta+}—H^{\delta-}$. *P. W. Selwood*, J. Catal. *42*, 148 (1976) supports such a view of H on nickel surfaces.
[43] For a discussion of the M—H bond in transition metal complexes see *J. P. Jesson* in *E. L. Muetterties:* Transition Metal Hydrides. Marcel Dekker, New York 1972, Chap. 3.
[44] *P. Meakin, J. P. Jesson, C. A. Tolman*, J. Am. Chem. Soc. *94*, 3240 (1972).
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[46] *B. J. Argento, P. Fitton, J. E. McKeon, E. A. Rick*, Chem. Commun. *1969*, 1427.
[47] This problem can be minimized with the isolation cell configuration (Fig. 4).
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Spiroconjugation

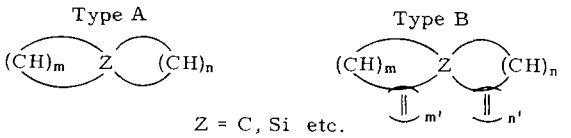
By Heinz Dürr and Rolf Gleiter[*]

Dedicated to Professor Georg Wittig

Spiro compounds having mutually perpendicular π-electron systems ("spiro-polyenes") exhibit a new kind of homoconjugation, which is designated as spiroconjugation. Spiro-polyenes are readily accessible, *e.g.* by cycloaddition, by elimination of dinitrogen from 1,2-diazaspiro-polyenes, and by cyclization of carbenium ions or carbanions. The magnitude of the effect exerted by spiroconjugation is estimated by model calculations. It can be detected, for instance, by comparison of the electronic and photoelectron spectra of spiro-polyenes and analogous compounds which are unable to undergo such interaction.

1. Introduction

Linkage of two cyclic systems by a central atom Z (Z=C, Si, *etc.*) gives rise to spiro compounds. If both rings contain π-electron systems we call the compounds *spiro-polyenes* or *spirenes* in order to avoid the complex systematic nomenclature. In principle, spiro-polyenes can be divided into two large groups A and B. In spiro-polyenes of type A only endocyclic double bonds are present, while molecules of type B also possess exocyclic double bonds. The CH groups can be replaced by hetero atoms.



Aa: m, n = odd (3, 5, 7)
Ab: m, n = even (2, 4, 6)
Ac: m = even (2, 4, 6, 8), n = odd (3, 5, 7)

B: m = even, n = even, m' = even or odd, n' = even or odd
Ba: $m = n = 0$, $m', n' = 2, 3, 4$
Bb: $m, n = 2, 4, 6, 8$, $m', n' = 1, 2, 3$
Bc: $m = 0$, $n = 2, 4, 6$, $m' = 2, 3, 4$, $n' = 1, 2, 3, 4$

As a result of their mutually perpendicular π-electron systems, spiro-polyenes exhibit a new kind of homoconjugation which has been termed spiroconjugation[1-5].

Spiroconjugation should be detectable by known physical methods and also manifest itself in the reactions of these compounds. Compounds of type Ac are an exception since the effect can only be observed in ions and radicals.

Aa  *(1)*
⊕, ⊖, •

Ab  *(2)*

Ac  *(3)*
⊕, ⊖, •

Ba  *(4)*

Bb  *(5)*

Bc  *(6)*

Apart from these theoretical aspects, spiro-polyenes are also of industrial interest. Hetero-spirenes of type A are photochromic systems which can undergo reversible photochemical (or also acid-catalyzed) ring opening. They have therefore been examined with regard to their utility in silver-free imaging systems and as memories in data display systems[6].

So far spiro-polyenes have only been found in partially hydrogenated form in nature; some of them are employed as drugs (*e.g.* griseofulvin)[7].

The present survey is concerned exclusively with fully conjugated spiro-polyenes of types A and B (for literature concerning partially saturated systems, see refs. [8, 9]).

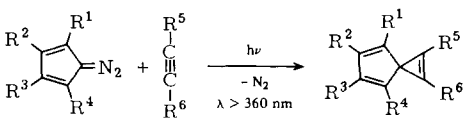
2. Syntheses of Spiro-Polyenes

2.1. Cycloaddition

In principle, spiro compounds can be synthesized in a very simple manner. One general approach is the [1,2] cycloaddition of suitable precursors (cycloalkenylidenes) to alkynes or benzene derivatives. This method gives: spiro[2.5]heptatriene *(9)*, spiro[2.4]octatrienone *(11)*, spiro[4.6]undecapentaene *(16)*, spiro[4.8]tridecahexaene *(18)*, and the dibenzo-annelated species spiro[5.8]tetradecahexaenone *(20)*. Some hetero spiro-polyenes are also obtained by cycloaddition.

2.1.1. [1+2] Cycloadditions of Cycloalkenylidenes

Photolysis of diazocyclopolyenes *(7)* gives cycloalkenylidenes (cyclic carbenes) which can undergo intermolecular [1+2] cycloaddition, *e.g.* to alkynes *(8)*. Spiro[2.4]heptatrienes *(9)* are formed in good yields by this reaction[10-13].



(7) *(8)* *(9a)-(9d)*

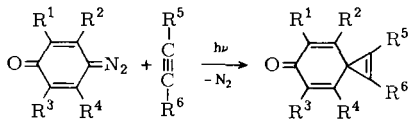
	$R^1=R^2$	R^3	R^4	R^5	R^6	Yield [%]
a	H	H	H	CH_3	CH_3	47
b	Cl	Cl	Cl	CO_2CH_3	CO_2CH_3	22
c	C_6H_5	—CH=CH—CH=CH—		H	CO_2CH_3	26
d	C_6H_5	C_6H_5	C_6H_5	CO_2CH_3	CO_2CH_3	40 [10]

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Substituted diazocyclopentadienes *(7)* have to be irradiated with long-wavelength UV light ($\lambda > 360$ nm) since secondary photoreactions of the products *(9)* will otherwise occur[11–13].

A related hetero spiro-polyene, 2,3-diphenylspiro[cyclopropene-1,1'-phthalan]-3'-one, was obtained by photolysis of benzocyclobutenedione in tolan; in this case 3-oxophthalan-1-ylidene undergoes [1+2] cycloaddition[14].

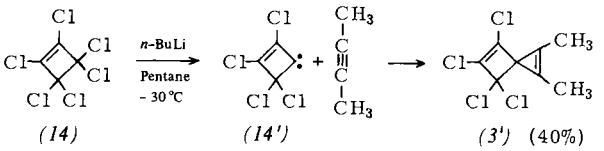
The cyclic carbene generated from the *p*-quinone derivative *(10)* reacts with alkynes *(8)* in the same way to give spiro[2.5]-octatrien-6-ones *(11)*[15,16].



(10) *(8)* *(11a), (11b)*

	R^1	R^2	R^3	R^4	R^5	R^6	Yield [%]
a	*t*-Bu	H	H	*t*-Bu	CH_3	CH_3	61 [15]
b	—CH=CH—CH=CH—		—CH=CH—CH=CH—		C_6H_5	CO_2CH_3	32 [16]

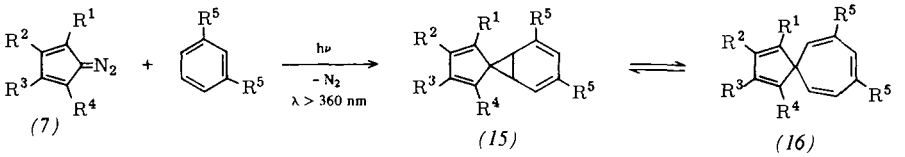
Heavy-metal catalyzed thermolysis of tetrachlorodiazocyclopentadiene *(7b)* in alkynes leads to the spiro[2.4]heptatrienes *(9)* in reasonable yields[17a]. No other examples of this reaction are known.



(14) *(14')* *(3')* (40%)

[1+2] Cycloaddition and valence-bond isomerization: Cycloalkenylidenes are capable of [1+2] cycloaddition with benzene or benzene derivatives—in a reaction resembling that with alkynes. A spiro-norcaradiene *(15)* is formed initially and subsequently yields spiro[4.6]undecapentaene *(16)* by thermal disrotatory ring cleavage[19]. The position of the equilibrium between *(15)* and *(16)* depends upon the substituents[19] (cf. [22,23]).

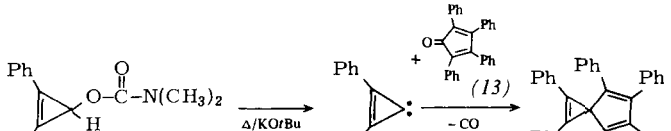
Extension of this synthesis to larger ring system by cycloaddition of cyclopentadienylidenes *(7')* to cyclooctatetraene does not lead to spiro[4.8]tridecahexaenes *(18)* but instead to the valence-bond isomers *(17)*. The NMR spectrum of the dibenzo derivative (42% yield) indicates an equilibrium between the valence-bond isomers *(17)* and *(18)* at higher temperatures.



(7) *(15)* *(16)*

R^1	R^2	R^3	R^4	R^5	*(15)*⇌*(16)*	Yield [%]
H	H	H	H	H	30—40	[21]
C_6H_5	C_6H_5	C_6H_5	C_6H_5	H	17	[19, 20]
C_6H_5	C_6H_5	C_6H_5	H	H	10	[19, 20]
Cl	Cl	Cl	Cl	H	40	[19, 20]
Cl	Cl	Cl	Cl	CF_3	47	[19, 20]
—CH=CH—CH=CH—		—CH=CH—CH=CH—		H	15	[19, 20]

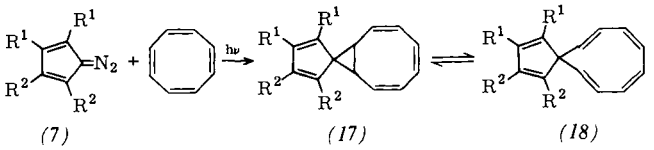
An interesting route *via* a cycloaddition of diphenylcyclopropenylidene *(12')* to tetracyclone *(13)* with concomitant C=O elimination also provides an entry to the spiro[2.4]heptatriene system *(9)*[17b].



(12) *(12')* *(9c)*

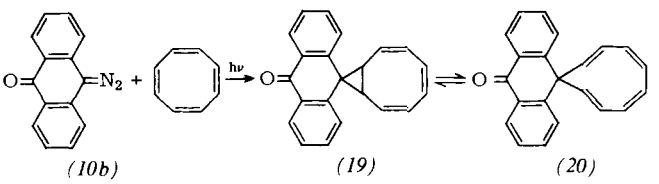
Attempted synthesis of the spiro[2.6]nonatetraene system *(33)* (see Section 2.2) by an analogous method was unsuccessful[18].

Cycloaddition of a carbenoid intermediate has been observed on treatment of hexachlorocyclobutene *(14)* with *n*-butyllithium. The intermediate tetrachlorocyclobutenylidene *(14')* undergoes [1+2] cycloaddition with 2-butyne to give 4,5,6,6-tetrachloro-1,2-dimethylspiro[2.3]hexa-1,4-diene[25].



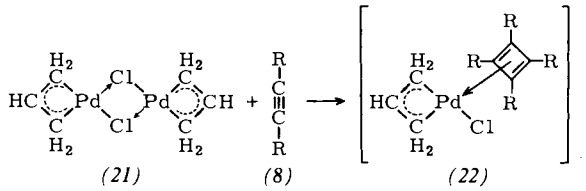
(7) *(17)* *(18)*

By analogy, the diazoanthrone *(10b)* reacts with cyclooctatetraene to give compound *(19)* which exists in equilibrium with the spiro[5.8]tetradecahexaene *(20)*[21,24].

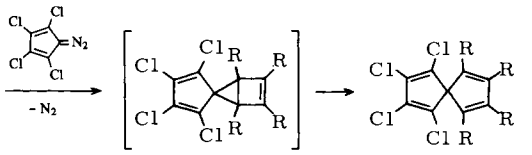


(10b) *(19)* *(20)*

An addition reaction between thermally generated tetrachlorocyclopentadienylidene to the Pd complex *(22)* (prepared from alkyne and $PdCl_2$) to form spiro[4.4]nonatetraenes *(24)*[17] has not been entirely elucidated.



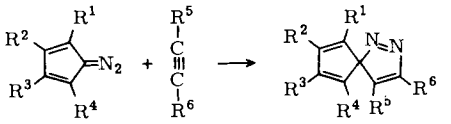
(21) (8) (22)



(23) (24a), R = CH_3, (16%) (24b), R = C_2H_5, 10%

be carried out at room temperature in aprotic solvents. Moreover, the 1 and ω positions of the diazocycloalkene should be substituted since 1,3-dipolar cycloadditions will otherwise be followed by [1,5] sigmatropic shifts even at room temperature.

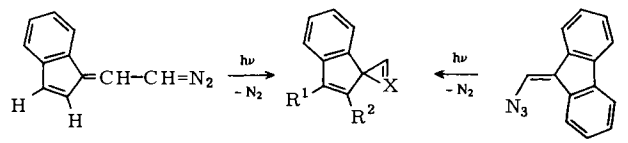
8-Oxa- and 8-thia-1,2-diazaspiro[4.5]decatetraenes *(31)*[32] and 1,2-diazaspiro[4.5]decatetraenones *(32)*[33] can be synthesized in similar manner.



(7) (8) (29)

R^1	R^2	R^3	R^4	R^5	R^6	Yield [%]
C_6H_5	C_6H_5	C_6H_5	C_6H_5	CO_2CH_3	CO_2CH_3	84 [28b]
C_6H_5	H	H	C_6H_5	$-(CH_2)_6-$		66 [28c]
—CH=CH—CH=CH—		—CH=CH—CH=CH—		CO_2CH_3	CO_2CH_3	82 [28a]
—CH=CH—CH=CH—		—CH=CH—CH=CH—		CF_3	CF_3	91 [29a]
—CH=CH—CH=CH—		—CH=CH—CH=CH—		CH_3	$N(C_2H_5)_2$	22 [29b]
C_6H_5	H	H	C_6H_5	—CH=CH—CH=CH—		45 [30]

Intramolecular cycloaddition of vinylcarbenes or vinylnitrenes: Photochemical elimination of N_2 from suitably substituted diazoalkenes such as *(25)* or vinyl azides such as *(27)* generates reactive carbene or nitrene intermediates which can undergo intramolecular cycloaddition to give spiro[2.4]heptatrienes *(9)* or their aza analogs *(26)*.



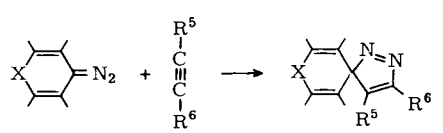
(25) (9f), (26) (27)

(25)→*(9f)*: X = CH; $R^1 = R^2$ = H : 21%[26]
(27)→*(26)*: X = N; $R^1 = R^2$ = —CH=CH—CH=CH— : 74%[27]

2.1.2. 1,3-Dipolar Cycloaddition

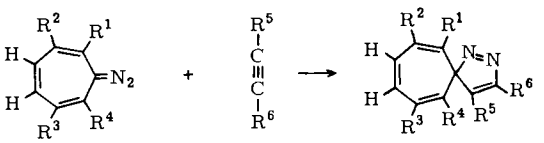
1,3-Dipolar cycloaddition of diazocycloalkenes to alkynes *(8)* leads exclusively to heterospiro-polyenes, or more precisely to diazaspiro-polyenes. This reaction has been studied in great detail. The yields of 1,3-dipolar cycloaddition are usually good to very good; the basic reaction has been known for some time[28a].

The diazocycloalkene acts as 1,3-dipole and the alkyne as dipolarophile. Examples are the reactions of *(7)* to give *(29)*, of *(28)*, X = —CH=CH—, O, or S, to give *(30)* or *(31)*, X = —CH=CH—, O, or S, and of *(10)* to give *(32)*, X = CO.



(7), (10), (28) (8) (29)-(32)

At higher temperatures, irreversible [1,5] sigmatropic rearrangements may occur; hence the reactions should ideally



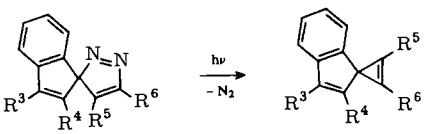
(28), X = —CH=CH— (8) (30)

R^1	R^2	R^3	R^4	R^5	R^6	Yield [%]
—CH=CH—CH=CH—		H	H	CO_2R	CO_2R	52 [31]
—CH=CH—CH=CH—		H	H		$-(CH_2)_6-$	80 [31]
—CH=CH—CH=CH—					$-(CH_2)_6-$	64 [31]

2.2. Elimination of Dinitrogen from 1,2-Diazaspiro-Polyenes

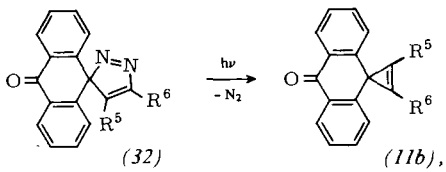
Another simple entry to spiropolyenes is provided by elimination of dinitrogen from 1,2-diazaspiro-polyenes *(29)*—*(32)*. In special cases this elimination can be induced thermally; however, the photochemical procedure is milder.

Secondary reactions can be avoided by use of mono- or dibenzo derivatives of the diazaspiro-polyenes *(29)*—*(32)*. Photochemical elimination of N_2 then occurs practically quantitatively and spiro-polyenes are formed in high yields. The route permits synthesis of spiro[2.*n*]polyenes only. Three examples are cited.



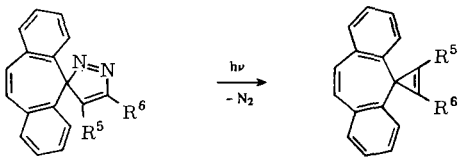
(29) (9g)-(9i)

	R^3	R^4	R^5	R^6	Yield [%]
g	C_6H_5	C_6H_5	$-(CH_2)_6-$		59 [34]
h	—CH=CH—CH=CH—		CH_3CO_2	CH_3CO_2	66 [35a]
i	—CH=CH—CH=CH—		CF_3	CF_3	86 [35b]



(32) (11b), (11c)

	R^5	R^6	Yield [%]
b	C_6H_5	CO_2CH_3	48 [33b] (thermal 78%)
c	CO_2CH_3	CO_2CH_3	64 [33a]

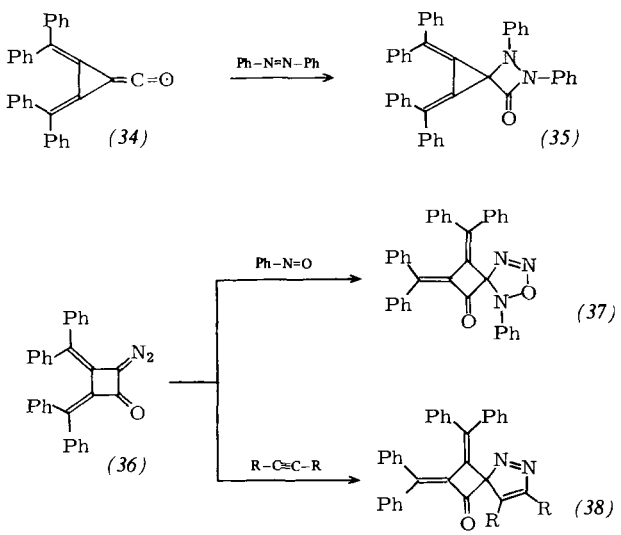


(30) $-R^5-R^6- = -(CH_2)_6-$ (33) (10%) [31]

Derivatives of spiro[2.5]octatriene were obtained in the same way[32].

If the cyclopentadiene ring of (29) bears only phenyl substituents then an alternative reaction occurs to give benzocyclopropenes[35c].

Cycloaddition of the ketene (34) with azobenzene gives spiro[2.3]hexenes (35)[35d] having exocyclic double bonds as in type Bc.



(34) (35) (37) (36) (38)

1,3-Dipolar cycloadditions of the diazo compounds (36) lead to spiro[3.4]octenes (37) and (38) which likewise correspond to the Bc type.

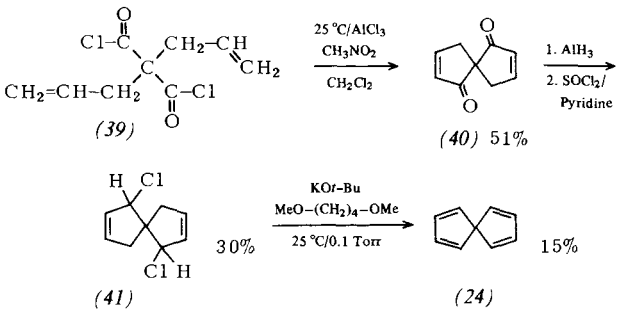
Hetero[2.5]-[35e] and hetero[4.5]spirenes[35f] were also obtained by cycloaddition.

2.3. Cyclization of Carbenium Ions or Carbanions

2.3.1. Cyclization of Carbenium Ions

A classical route to spiro-polyenes starts from cyclization of suitable carbenium ions. The cyclization product often has to be transformed into the spiro-polyene in a series of steps—usually elimination reactions. This synthetic approach is therefore less direct and generally gives lower yields than cycloaddition and cycloelimination.

The synthesis of the unsubstituted spiro[4.4]nonatetraene (24) is shown schematically as an example[36].



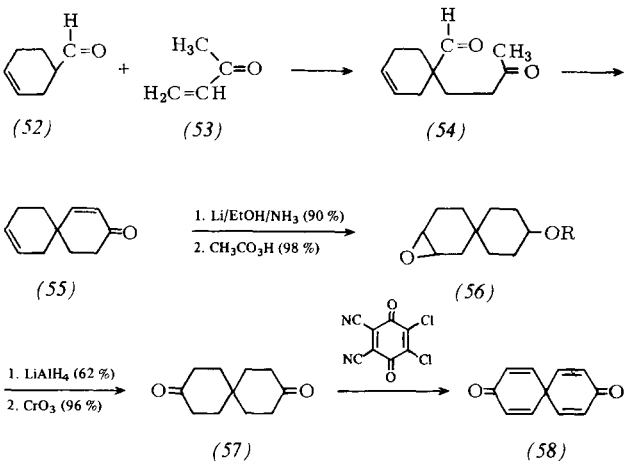
(39) (40) 51% (41) 30% (24) 15%

Analogous examples are compiled in Table 1. Other known spiro-polyenes include a dibenzo-annelated tetraazaspiro[4.4]nonadiene[39e] and a monobenzotetraoxa[5.5]spiropolyene[39f]; tetraoxa[6.6]spiro-polyenes are also known[39g].

In formation of the spiro compound on treatment of pentaerythritol tetrabromide with sodiomalonic ester an S_N reaction occurs as the crucial step[40]. Decarboxylation and subsequent elimination (Hofmann degradation or Cope elimination) gives spiro[3.3]heptadiene[41].

2.3.2. Cyclization of Carbanions

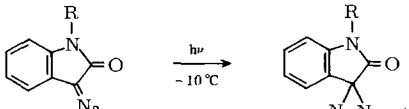
An intramolecular aldol reaction occurring as the decisive reaction step (54)→(55) in spiro-polyene formation plays an important role in the synthesis of spiro[5.5]undecatetraenedione (58)[42].



(52) (53) (54) (55) (56) (57) (58)

2.4. Other Synthetic Methods

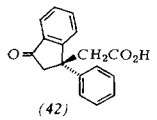
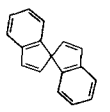
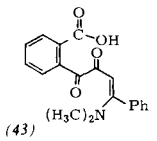
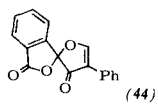
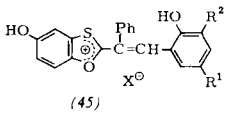
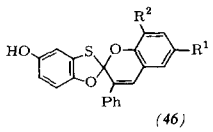
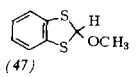
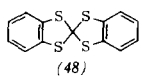
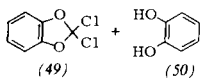
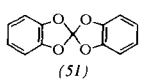
Spiro compounds can also be formed by valence-bond isomerization. A remarkable example is seen in the photochemical valence-bond isomerization of the diazo ketone (59) to the triazaspiro[2.4]heptadienone derivative (60)[43].



(59) (60)

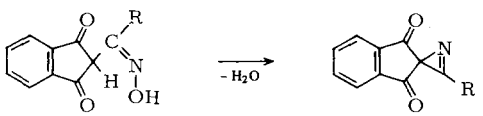
R = H: 5%; R = CH_3: 11%

Table 1. Synthesis of spiro[4.4]- and -[4.5]polyenes by cyclization of carbenium ions.

Starting compound(s)	Reagents Conditions	Spiro-polyenes	Yield [%]	Ref.
 (42)	[a]	 (24c)	[a]	[37, 38]
 (43)	H^+	 (44)	63	[39a]
 (45)	Base	 (46)	26–96	[39b–39f]
 (47)	200 °C Base	 (48)	15	[39c]
 (49) (50)	Δ	 (51)	96	[39d]

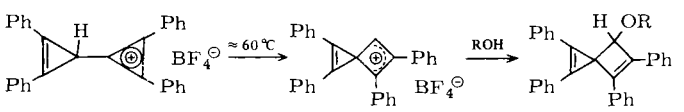
[a] 1) $SOCl_2/AlCl_3$, yield = 35 %. 2) $NaBH_4$. 3) Δ (gas chromatography), yield 2 + 3 = 55 %.

Dehydration can convert oximes into azaspiro[2.4]heptadienedione derivatives.



R = C_6H_5, CH_3

An extremely interesting route to spiro-polyenes is provided by the rearrangement of carbenium ions. Thermally induced rearrangement of the 1,2-diphenyl-3-(2,3-diphenyl-2-cyclopropenyl)cyclopropenylium ion in refluxing CH_2Cl_2 proceeds *via* ring expansion to give the spiro[2.3]hexadienylium ion *(3)*. This species can be trapped with water or methanol as a spiro[2.3]hexadiene derivative[44]. Further syntheses are enumerated in ref. [45].



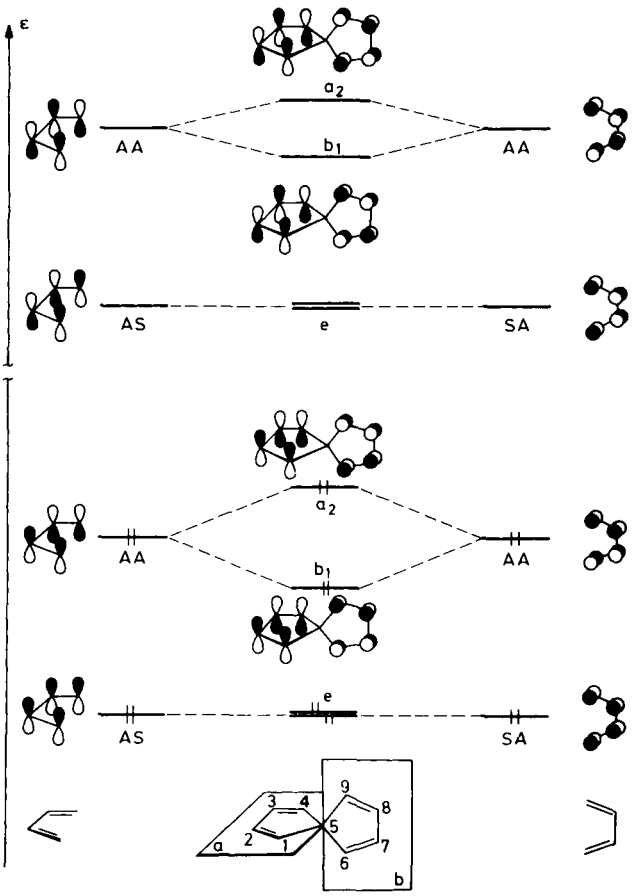
(3)

(3'), R = H : 51%
R = CH_3 : 68%

3. Model Calculations

Let us consider the phenomenon of spiroconjugation in unsubstituted spiro[4.4]nonatetraene *(24)* (type Ab, $m = n = 4$) with the aid of a qualitative interaction diagram.

The four π orbitals of the butadiene fragment are shown on the left and right of Figure 1, and characterized



(24)

Fig. 1. Qualitative interaction diagram for two mutually perpendicular butadiene moieties (spiro[4.4]nonatetraene *(24)*). The symbols A and S denote antisymmetric and symmetric, respectively, with reference to the planes a and b.

with respect to the two planes a and b. The symbols A and S mean antisymmetric and symmetric, respectively, with respect to the planes of symmetry[*].

Symmetry considerations reveal that only those orbitals which are antisymmetric to both planes of symmetry (AA) can interact with each other. In the case of *(24)* the occupied and the unoccupied orbitals each give two linear combinations which belong to the irreducible representations b_1 and a_2 in the D_{2d} point group. These two linear combinations are shown as Newman projections in Figure 2.

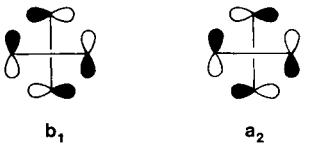


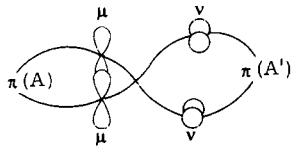
Fig. 2. Phase relationship of orbitals b_1 and a_2 of *(24)* (Newman projection).

The reason for the splitting of the AA level in the interaction diagram (Fig. 1) lies in the spatial interaction of the 2p atomic orbitals of centers C^1 and C^4 with those of C^6 and C^9[**].

The splitting between the two highest occupied levels in *(24)* is found by Extended-Hückel and MINDO/3 calculations to be *ca.* 0.6 eV[46, 47].

Generalizing, only those orbitals of the π system will interact which possess an odd number of nodal planes. Referred to the planes a and b of Figure 1 this means that they must possess the symmetry designation AA.

With the aid of perturbation theory[48] it can be deduced that the spiro-interaction of two mutually perpendicular π systems (π(A) and π(A')) is all the greater, the greater the



interaction integral $\beta^{\mu\nu}_{spiro}$ and the smaller the energy difference between the basis orbital energies of the interacting orbitals.

$$\beta^{\mu\nu}_{spiro} = \langle \pi^{\mu}(A)/H/\pi^{\nu}(A') \rangle$$

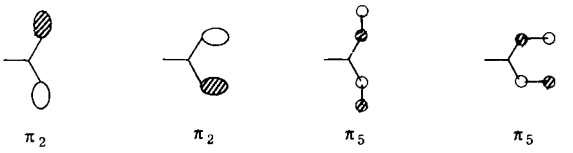
The requirement that $\beta^{\mu\nu}_{spiro}$ should be as large as possible has its limitations in that the centers μ and ν cannot approach each other at will.

The second condition for maximum spiro-interaction, *i.e.* keeping the energy difference between the basis orbitals of the systems A and A' as small as possible, favors spiro systems with D_{2d} symmetry (π(A)=π(A')).

Figure 3 shows the π-orbital diagrams of *(1)*, *(4)*, *(9)*, and *(61)* to *(64)* before and after spiroconjugation. Comparison of the interaction diagrams in Figures 1 and 3 confirms the above statement: interaction is large only when the two subsystems are identical (π(A)=π(A'); D_{2d} symmetry). If π(A)≠π(A'), as in *(9)*, *(61)*, and *(62)*, spiroconjugation is only slight and may be masked by other effects, as shown by the example of the spiroheptatriene *(9)*[48].

Comparison of the MO diagrams of *(4)* and *(24)* shows that the greater splitting of the occupied AA orbitals is found in *(24)*, while the greater splitting of the unoccupied AA orbitals is found in *(4)*. These results can also be understood in terms of perturbation theory. While the energies of the basis orbitals of the butadiene subsystems in *(24)* and *(4)* are equal to a first approximation, the coefficients differ at the linkage sites in the corresponding wave functions.

In *(63)* and *(64)*, on the other hand, the coefficients at the coupling sites of the wavefunctions bearing the symmetry designation AA are of equal magnitude; identical interaction diagrams therefore result.



The systems of greatest interest to the chemist are those in which spiroconjugation leads to a stabilization of the ground state. In *(62)* the HOMO is stabilized by spiroconjugation (Fig. 3). Charge delocalization extending over the five-membered ring can thus take place.

Another system predicted to be stabilized is *(1)*[2] (cf. Fig. 3). This stabilization is particularly extensive[2] if the following relation is satisfied for a spiro compound of type Aa:

$$m = n = 4q + 3 \quad \text{for } q = 0, 1, \ldots$$

Only in these systems does the highest singly occupied orbital of the subsystems *m* and *n* possess AA symmetry. As a result of spiro conjugation, the B_1 linear combination of the two wave functions is stabilized and the A_2 linear combination destabilized. The interaction can be so large that the singlet state of the corresponding biradical is stabilized relative to the triplet state. Thus, model calculations on *(1)* by the PPP-CI method[2] have shown, for example, that the singlet state ($^1A_1$) is 0.64 eV more stable than the lowest-lying triplet state ($^3B_2$). MINDO/3 calculations with reduced CI, on the other hand, show an energy difference of 0.63 eV in favor of the $^3B_2$ state[47].

All valence electron methods confirmed the concepts[1, 2] derived from π approximations[3, 46, 47]; however, comparison of experimental and theoretical results[46] showed that the spiro-interaction is predicted as being too small. The geometries of spiro compounds[47, 49] predicted by the MINDO/3 method are in good agreement with experimental data. Model calculations performed in connection with spectroscopic studies will be considered in the following Sections.

4. Spectroscopic Detection of Spiroconjugation

Proof of spiroconjugation by molecular spectroscopy generally consists in a comparison between the spectrum of the spiro compound and that of a reference substance without spiroconjugation.

[*] Construction of the interaction diagram of Fig. 1 requires that only orbitals of the same symmetry interact.

[**] The overlap integral is calculated to be 0.025 for the distances between C^1 and C^6 and C^4 and C^9 (2.51 Å). The relatively large interaction between the AA levels can be rationalized as arising four times.

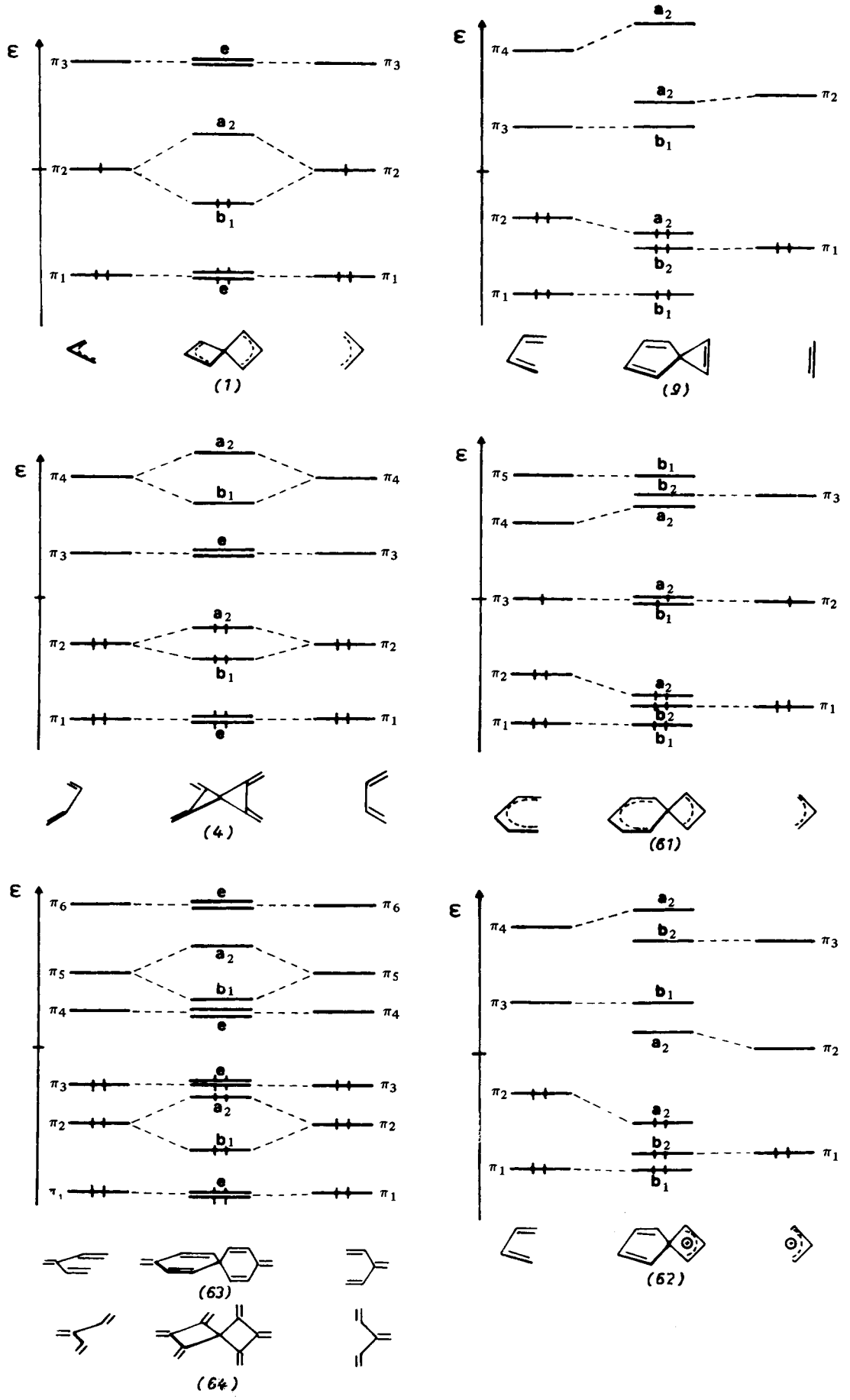
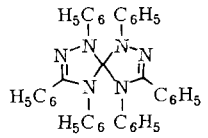


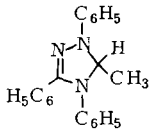
Fig. 3. Qualitative interaction diagrams for the spiro systems *(1)*, *(4)*, *(9)*, and *(61)* to *(64)*.

4.1. Electronic Absorption Spectroscopy

The spiroconjugation model proved of value in discussions of the electronic spectra of 3,3'-spirobis(triazoline) *(65)*[50]. The electronic spectrum of *(65)* exhibits a hypsochromic shift of the longest wavelength band by 2500 cm^{-1}[51] relative to the first band of the electronic spectrum of *(66)*.



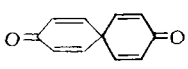
(65)



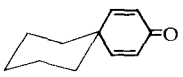
(66)

The electronic spectra of some ketals derived from cyclopentadienones, cyclopropenones, and tropone revealed shifts of the longest wavelength bands to longer (cyclopentadienone derivatives) and to shorter wavelengths (cyclopropenone and tropone derivatives), respectively, on comparison with the corresponding dialkyl compounds[1]. These observations could also be readily explained in terms of the spiro model: the HOMO is destabilized by spiro-interaction in the cyclopentadienone ketals, and stabilized in the other two cases.

Further examples of spiroconjugation were discovered on comparison of the electronic spectra of spirobi(indene) *(24c)* and indan[37], of spiro[5.5]undeca-1,4,7,10-tetraene-3,9-dione *(58)* and spiro[5.5]undeca-1,4-dien-3-one *(67)*[52], of *(24)* and spiro[4.4]nona-1,3-diene *(68)*[36,53], and of spiro[2.4]-heptatriene *(9)* and spiro[2.4]heptadienes[11b,12].



(58)



(67)

On comparison of *(58)* and *(67)* a bathochromic shift of the second $\pi^* \leftarrow \pi$ band by 7400 cm^{-1} is observed. From this a value of $\beta' \approx -0.5$ eV may be calculated for the spiro resonance integral.

In contrast to these findings, the electronic spectra of fluorene, 9,9'-spirobi(fluorene) *(24d)*, and its doubly bridged derivative [6.6]vespirene can be interpreted without invoking spirointeraction in *(24d)*[54].

4.2. Photoelectron Spectroscopy

Provided that Koopmans' theorem $(-\varepsilon_J = I_{V,J})$[55] holds[*], photoelectron spectroscopy is the method of choice for demonstrating the presence of spiroconjugation. The examples studied so far are 3,3-divinyl-1,4-pentadiene ("tetravinylmethane")[56], tetravinylsilane[57], 9,9'-spirobi(fluorene) *(24d)*[58], 1,1'-spirobi(indene) *(24c)*[59], 1,4,6,9-tetrathiaspiro[4.4]nonane[60], as well as the unsubstituted compounds *(24)*[53] and *(9)*[49]. Interaction effects between 0.3 and 1.5 eV were recorded for systems having D_{2d} symmetry. As a result, the spiro resonance integral can be estimated as $\beta' \approx 0.2$—0.3 eV considering the coefficients of the wave function[52,59,60].

Of particular interest are studies on *(24)*. The experimental energy difference between the first two ionization potentials (1.23 eV) corresponds to the energy difference between the first two bands in the electronic absorption spectrum of this compound. Owing to the high symmetry (D_{2d}) of *(24)*, the Coulomb and the exchange integrals for the first two electron transitions ($8e \leftarrow 1a_2$ and $8e \leftarrow 1b_1$) can be neglected[53]. This means that $\Delta E = \Delta I$ in this case, *i.e.* the experimental energy difference (ΔE) between the first two bands in the electronic absorption spectrum is equal to the difference (ΔI) between the first two ionization potentials. This could be demonstrated by comparison of the electronic absorption and PE spectra of *(24)* with those of spiro[4.4]nona-1,3-diene *(68)* (Fig. 4): the electronic absorption spectrum (Fig. 4b) of *(68)* contains only *one* band between 30×10^3 and 55×10^3 cm^{-1}, namely that at 39.5×10^3 cm^{-1} corresponding to the $\pi_3 \leftarrow \pi_2$ transition. In contrast, the electronic absorption spectrum of *(24)* shows *two* bands at 37.0×10^3 cm^{-1} and 48.0×10^3 cm^{-1}. These two bands correspond to the $8e \leftarrow 1a_2$ and $8e \leftarrow 1b_1$ transitions, the energy difference being 1.23 eV.

A similar situation is found in the PE spectra of compounds *(24)* and *(68)* (Fig. 4c). The band at 8.38 eV in the PE spectrum of *(68)* is due to ionization from π_2. In the case of *(24)* there are two bands (7.99 and 9.22 eV) in the PE spectrum

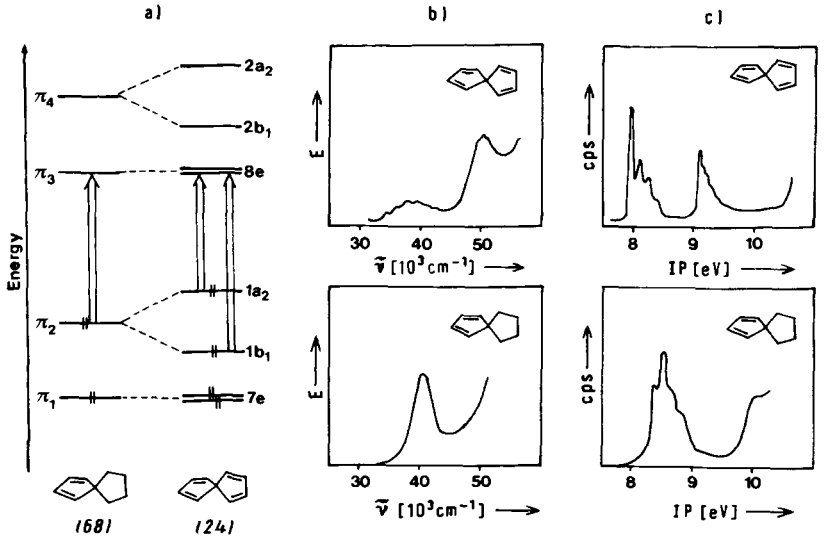


Fig. 4. a) HMO diagram of the highest occupied and lowest unoccupied π-MOs for *(68)* and *(24)*; b) electronic absorption and c) photoelectron spectra of *(24)* and *(68)*.

[*] This theorem assumes that the ground state of a molecule and the states of the corresponding radical cations can be described by the same molecular orbitals.

which are assigned to ionization processes starting from $1a_2$ and $1b_1$. The energy difference between the two bands is 1.23 eV.

4.3. NMR and ESR Spectroscopy

A change in net charge in the spiro compound as compared with the corresponding monocycle is predicted as a result of spiro-interaction[1, 47]. It is, however, impossible to establish a direct correlation between the measured ^{13}C chemical shift and the charge densities calculated by the MINDO/3 procedure in the case of *(24)*, *(68)*, *(9)*, *(16)*, and spiro[2.4]hepta-4,6-diene[61]. A schematic survey is presented in Figure 5.

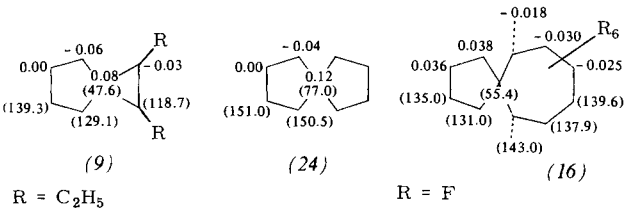


Fig. 5. Charge densities according to MINDO/3 and measured ^{13}C-NMR shifts of the spiropolyenes 1,2-diethyl(methyl)spiro[2.4]hepta-1,4,6-triene [type *(9)*], spiro[4.4]nona-1,3,6,8-tetraene *(24)* [36], and 6,7,8,9,10,11-hexafluorospiro[4.6]undeca-1,3,6,10-pentaene [type *(16)*]. The charge densities were calculated for the parent compounds [47]. $\delta(^{13}C)$ is given relative to TMS = 0.

The radical anions of *(58)* and *(67)*[62] and of spirobi(fluorenes) *(24d)* can be studied by ESR spectroscopy[63]. In no case could spiroconjugation be detected, because the unpaired electron occupies an orbital which is unaffected by spiroconjugation.

5. Reactivity

A significant change in reactivity as compared with a reference system without spiroconjugation is expected in spiro systems of type Ab having $m=n$, *e.g. (24)*, only in those cases where the HOMO or the LUMO is influenced by spiroconjugation. For instance, the HOMO should be destabilized in *(24)* and the LUMO stabilized in spiro[2.2]pentadiene *(2)*.

However, spiroconjugation not only alters the energies of the interacting levels but actually modifies the corresponding wave functions. The AO coefficients in the wave functions of the spiro systems which are antisymmetric with reference to the planes a and b (AA) should be smaller than in the wave functions of the isolated subsystems.

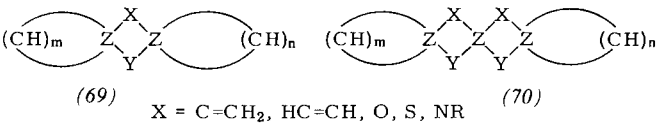
The two kinds of changes, that of the energy levels and that of the wavefunctions, have opposing effects on reactivity. Destabilization (stabilization) of the HOMOs (LUMOs) would lead to greater reactivity towards electrophiles (nucleophiles) and *vice versa*. However, the decrease of the coefficients mentioned above should reduce the extent of interaction.

Only few studies on the reactivity of spiro compounds have been published so far. There is no indication of the expected greater reactivity of *(24)* towards dienophiles, but a pronounced tendency to undergo dimerization is observed[36]. A theoretical interpretation of these observations has recently been proposed on the basis of perturbation theory[46]. Apart from *(24)*, cycloadditions were also found in the case of *(9)*[11]. Interestingly, *(24)* undergoes thermal rearrangement to indene[64], and thermolysis of *(16)* affords phenylcyclopentadiene[65]. Diels-Alder reactions have not been observed with *(16)*[32].

6. Outlook

The results available so far show spiro compounds to be an interesting field of study for synthetic and physical chemists.

Since the spiro effect was postulated eleven years ago, mainly bicyclic spiro-systems have been synthesized to explore the limitations of this concept. Very recently, reports have appeared about the synthesis of polycyclic systems[66, 67] derived from *(69)* and *(70)*.



It is remarkable that only few structural investigations[43a, 45b, 67c, 68] have been published, in spite of numerous spectroscopic studies (see Fig. 6).

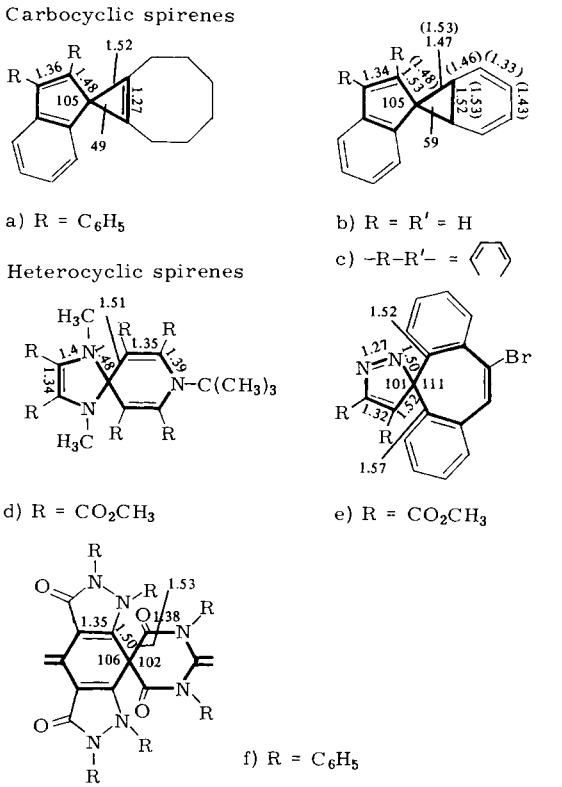
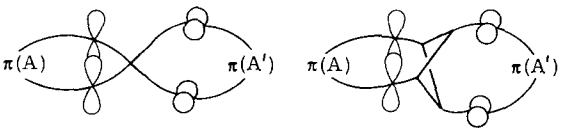


Fig. 6. Bond lengths [Å] and angles [°] in spiro-polyenes with and without hetero atoms. Values for c) are given in parentheses.

Proposals aiming to increase the interaction occurring in mutually perpendicular π systems are of interest. These include the incorporation of central atoms Z with low-lying d-orbitals[69] or replacement of spiro interaction by through-bond interaction[47, 70]. This brief survey shows that spiro compounds and spiro interactions are promising research topics.



Spiroconjugation Through bond

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New synthetic methods (25)

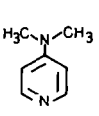
4-Dialkylaminopyridines as Highly Active Acylation Catalysts[1, 2]

By Gerhard Höfle, Wolfgang Steglich, and Helmut Vorbrüggen[*]

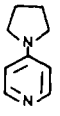
The synthesis of 4-dialkylaminopyridines can be accomplished in two steps starting from pyridine. Compared to pyridine, these derivatives are approximately 10^4 times more active when used as acylation catalysts. Dialkylaminopyridines are being used with ever-increasing frequency for acylation reactions which proceed either incompletely or not at all in pyridine. This article reviews the various possible applications of 4-dialkylaminopyridines in terpene, steroid, carbohydrate and nucleoside chemistry as well as in the transformation of amino acids into α-acyl aminoketones and polymerization of isocyanates. In addition, *N*-substituted 4-dialkylaminopyridinium salts can be used for the transfer of sensitive groups to nucleophiles in aqueous medium. The exceptional catalytic effect of these derivatives, even in non-polar solvents, is due, in part, to the formation of high concentrations of *N*-acylpyridinium salts which are present in solution as loosely-bound, highly reactive ion pairs.

1. Introduction

The reaction of acetic anhydride/pyridine with hydroxy compounds is a mild, dependable and general method for the preparation of the corresponding acetates. This procedure was first developed in 1901 by *Verley* and *Bölsing*[3] for the quantitative determination of terpene alcohols in essential oils and the method was successfully extended by *Emil Fischer* and *Bergmann*[4] to carbohydrate chemistry. The esterification of hydroxy compounds with acid chlorides was also found to proceed better in the presence of pyridine[5].



DMAP



PPY

In 1967, *Litvinenko* and *Kirichenko*[6] found in the course of kinetic studies (which became known at a somewhat later date) that replacing pyridine by 4-dimethylaminopyridine (DMAP) resulted in a rate increase of *ca.* 10^4 for the benzoylation of *m*-chloroaniline. Independent of this group, *Steglich* and *Höfle*[7] described in 1969 the extremely strong catalytic effect of DMAP and 4-pyrrolidinopyridine (PPY) in prepara-

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tive scale acylations, thereby providing the impetus for the broad-scale use of these acylation catalysts. The enormous increase in reaction rate is illustrated by the following comparison:

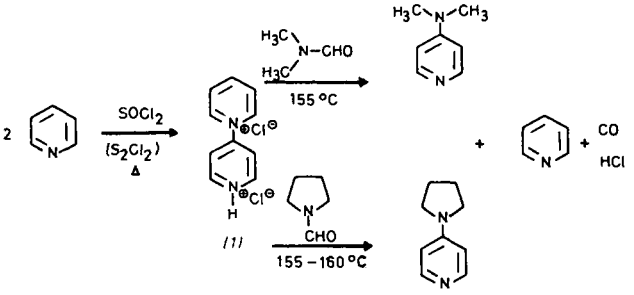
Equimolar quantities of anhydrous or 96% ethanol (29 ml, 0.5 mol) and acetic anhydride (47 ml, 0.5 mol) are mixed in two Erlenmeyer flasks with stirring and to the first flask is added pyridine (8 ml, 0.1 mol). Within 3–4 min the reaction mixture begins to boil. When a solution of DMAP (0.6 g, 0.005 mol) dissolved in a small amount of ethanol is added to the second flask, the solution begins to boil spontaneously under esterification.

Since the development of a convenient and economic procedure for the preparation of 4-dialkylamino-substituted pyridines by *Vorbrüggen et al.*[2], these new catalysts, DMAP and PPY[8], have become available in any desired amount.

2. Preparation

Dimethylaminopyridine (DMAP) was first obtained by reaction of 4-chloropicolinic acid with dimethylamine followed by decarboxylation[9]. Almost all later syntheses started with pyridine substituted at the 4-position. Such methods, however, are not suitable for the preparation of DMAP on a technical scale[2].

An economic technical synthesis of DMAP in ton quantities under normal pressure became possible as a result of the recently discovered transformation of 1-(4-pyridinio)pyridinium dichloride *(1)* (easily prepared[10–13] by reaction of thionyl chloride with pyridine) with *N,N*-dimethylformamide (DMF) at 140–160 °C. The yield of DMAP lies in the range of 65–70%, based on thionyl chloride[2]. The analogous reaction of *(1)* with *N*-formylpyrrolidine gives 4-pyrrolidinopyridine (PPY)[2,8,14] in similar yields.



DMAP (m.p. 112–113 °C) and PPY (m.p. 57—58 °C)[14] are colorless, crystalline substances which are very soluble in methanol, ethyl acetate, chloroform, methylene chloride, 1,2-dichloroethane, acetone, and acetic acid and less soluble in cold hexane, cyclohexane, and water. DMAP can be recrystallized from ethyl acetate and PPY from pentane or hexane.

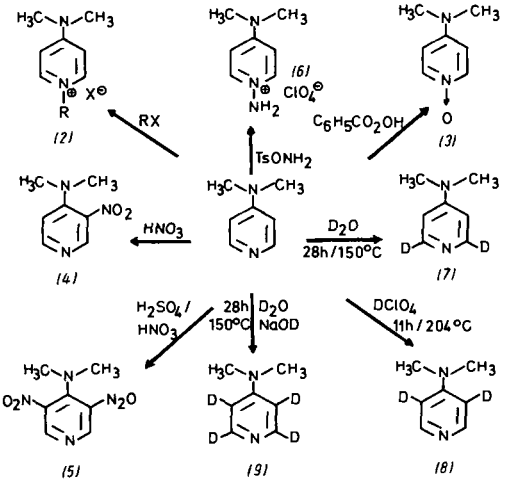
The basicities of DMAP[15–24] and PPY[23] in water as well as the dipole moment of DMAP[25–27] in benzene and dioxane have been determined by several groups. Of especial interest are the thermodynamic investigations concerned with the protonation of DMAP in water[18] and calculations whereby the influence of substituents on the basicity has been determined[24,27,28].

pK_a (DMAP) = 9.70 (20 °C)[19]
(PPY) = 9.90 (20 °C)[23]
dipole moment: DMAP = 4.31 D (benzene, 25 °C)[26]

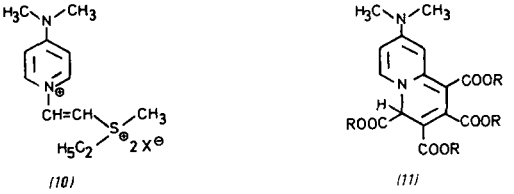
In addition, the UV[15–17,22,29–31] and NMR spectra[18,19,32–37] have been measured and analyzed. There is a characteristic bathochromic shift in water [λ_{max} = 259 nm ($\log\varepsilon$ = 4.26)] on protonation of the ring nitrogen [λ_{max} = 280 nm ($\log\varepsilon$ = 4.24)][16].

3. Chemical Reactions

DMAP reacts readily with electrophilic reagents. It is possible to quaternize DMAP in high yield with either methyl iodide or ethyl bromide to *(2)*, R = CH_3 or C_2H_5[38,39]. *(2)*, R = CH_3, decomposes quantitatively in the presence of aqueous alkali to *N*-methyl-4-pyridone[38].



On reaction with perbenzoic acid the strongly polar *N*-oxide *(3)*, m.p. 214—215 °C, is formed[15,40]. Nitration of DMAP with HNO_3/H_2SO_4 gives the 3-nitro derivative *(4)* in 81% yield and, under forcing conditions, the 3,5-dinitro compound *(5)* is obtained[37,41]. Reaction with *O*-(*p*-toluenesulfonyl)hydroxylamine affords the *N*-amino compound *(6)* in 67% yield which is isolated as the perchlorate[42]. By treatment with D_2O it is possible to selectively exchange the α-protons in DMAP to give *(7)*, with $DClO_4$ to exchange the β-protons to furnish *(8)*, and with D_2O/NaOD to replace all aromatic protons by deuterium to yield *(9)*[43].



Addition of DMAP to *S,S'*-diethyl-*S,S'*-dimethyl-*S,S'*-1,2-vinylenedisulfonium salts results in the smooth formation of the salt *(10)* with concomitant generation of ethyl methyl sulfide[44]. Reaction of DMAP with acetylenedicarboxylic acid leads spontaneously to the bis-adduct *(11)* in high yields[45].

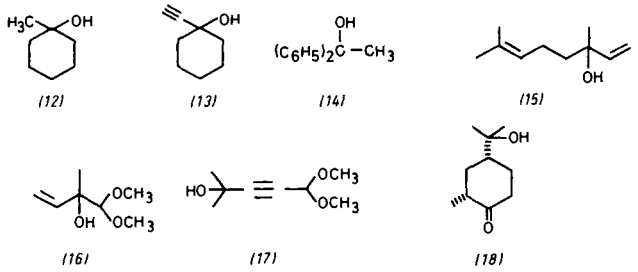
4. Applications as Acylation Catalysts

4.1. Acylation of Alcohols

The high catalytic activity of DMAP and PPY can be used for acylating sterically-hindered secondary or tertiary alcohols

with carboxylic anhydrides or acyl halides when the pyridine method fails. In most cases, it is necessary to use only 0.05—0.2 mol of catalyst per mol of substance and the acid which is formed can be bound with an equivalent amount of triethylamine[1, 7] or pyridine[46]. Such solvents as hexane, toluene, benzene, methylene chloride, chloroform, ethyl acetate, tetrahydrofuran, triethylamine, pyridine, or acetic anhydride are suitable for use with these catalysts.

Among the tertiary alcohols which can be easily acylated with DMAP and PPY, mention should be made of 1-methyl-



(12) (13) (14) (15) (16) (17) (18)

cyclohexanol *(12)*, 1-ethynylcyclohexanol *(13)*, 1,1-diphenylethanol *(14)*, linalool *(15)*, 1,1-dimethoxy-2-methyl-3-buten-2-ol *(16)*, 5,5-dimethoxy-2-methyl-3-pentyn-2-ol *(17)*, and *cis*-4-(1-hydroxyisopropyl)-2-methylcyclohexanone *(18)* (Table 1). The mild reaction conditions allow the acetylation of *(16)* and *(17)* to be performed with preservation of the acid-labile acetal function. *Bohlmann et al.*[51] have utilized PPY in pyridine for the acetylation of sensitive terpene and polyacetylene alcohols.

Linalyl acetate:

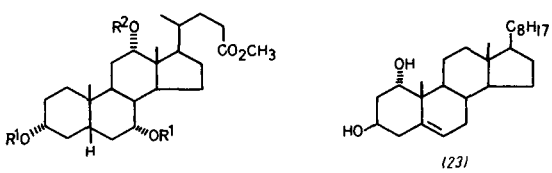
A mixture of linalool *(15)* (7.7 g, 50 mmol), triethylamine (10 ml, 75 mmol), acetic anhydride (7.6 g, 75 mmol), and DMAP (0.5 g, 4 mmol) is allowed to stand for 14 h at 24 °C. The solution is partitioned between ether and 2 N HCl, the organic phase is washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated *in vacuo*; yield: 7.9 g (80 %); b.p. 100 °C/10 torr.

Formylation with a mixture of formic acid and acetic anhydride can also be accelerated to an extraordinary extent by using DMAP and PPY as catalysts. Even tertiary alcohols such as *(13)* can be selectively formylated under basic conditions when the reaction temperature is kept below −30 °C to prevent decomposition of formic acid to carbon monoxide[23].

1-Ethynylcyclohexyl formate

1-Ethynylcyclohexanol (0.62 g, 5 mmol), formic acid (0.45 ml, 12 mmol), triethylamine (3.2 ml, 25 mmol), and DMAP (0.5 g, 4 mmol) are dissolved in 40 ml methylene chloride and the solution is cooled to −40 °C. Acetic anhydride is then added and the mixture is stirred at −35 °C for 30 min and thereafter allowed to slowly warm to room temperature over 1 h. The reaction solution is extracted with 2 N HCl followed by saturated $NaHCO_3$ solution, dried over $MgSO_4$ and distilled *in vacuo*; yield: 0.55 g (72 %), b.p. 90 °C (oven)/10 torr. The product contains less than 0.5 % of *(13)* and its corresponding acetate.

In the steroid series, there are numerous instances where DMAP and PPY have been used successfully as acylation catalysts. When methyl cholate *(19)* is reacted with acetic anhydride/pyridine, the hydroxy groups at the 3- and 7-position are preferentially acetylated to form the diacetate *(20)*[52]. When PPY is used, the axial 12α-OH group is also rapidly acetylated and, after 2 h reaction time at 24 °C, the triacetate *(21)*[1] is formed quantitatively. A mixture of formic acid and acetic anhydride yields the triformate *(22)*[53] under DMAP catalytic conditions. It is even possible to acetylate both hydroxyl groups of 1α-hydroxycholesterol *(23)* with acetic anhydride/DMAP at room temperature[54].



(19), $R^1 = R^2 = H$; (20), $R^1 = Ac$, $R^2 = H$
(21), $R^1 = R^2 = Ac$; (22), $R^1 = R^2 = CHO$

(23)

Methyl 3α,7α,12α-triformylcholate (22):

Methyl cholate *(19)* (1.7 g, 4 mmol), DMAP (0.5 g, 4.1 mmol), triethylamine (8 ml, 58 mmol), and formic acid (1 ml, 20 mmol) are dissolved in 100 ml dichloromethane and cooled to −15 °C. Acetic anhydride (6 ml, 63 mmol) is added dropwise with stirring to the reaction solution over 30 min and the mixture is then stirred for an additional 30 min at 0 °C. After addition of a few ml of methanol, the solution is evaporated *in vacuo* and the residue is dissolved in ethyl acetate. The resulting solution is washed with 1 N HCl followed by saturated $NaHCO_3$ solution; the organic layer is then dried over $MgSO_4$ and evaporated *in vacuo*. The residue consists of 2.0 g (97 %)

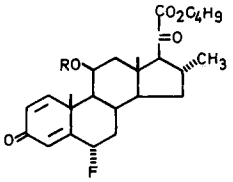
Table 1. DMAP- and PPY-catalyzed acylation of tertiary alcohols with carboxylic anhydrides.

Alcohol	Carboxylic anhydride	Catalyst/auxil. base	t [h]	T [°C]	Yield [%]	Ref.
(12)	$(Bz)_2O$	DMAP/NEt_3	13	80 [a]	87	[1]
(13)	$(C_2H_5CO)_2O$	DMAP/NEt_3	1	24 [a, b]	94	[1]
(14)	Ac_2O	PPY/NEt_3	40	24 [a]	92	[47]
(15)	Ac_2O	DMAP/NEt_3	14	24 [a]	80	[1]
(16)	Ac_2O	PPY/NEt_3	12	24 [a]	86	[48]
(17)	Ac_2O	DMAP	0.5	24 [c]	92	[1]
(18)	Ac_2O	DMAP	7	24 [d]	95	[49]
(18)	Ac_2O	pyridine	18	110 [e]	81	[50]
(13)	Ac_2O/HCO_2H	DMAP/NEt_3	1.5	−30 [c]	72	[23]

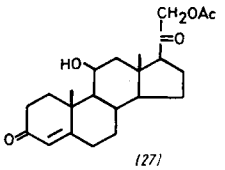
[a] Without solvent. [b] Exothermic reaction. [c] In CH_2Cl_2. [d] In NEt_3. [e] In toluene.

of (thin-layer chromatographically) pure *(22)* as an amorphous powder.

The axial 11β-OH group in *(24)* can be acylated with either acetic anhydride or butyric anhydride in pyridine in the presence of DMAP within 16 h at 27 °C to give *(25)* or *(26)*, respectively[55]. With formic acid/acetic anhydride/DMAP, the 11β-OH group in *(27)* can be formylated under basic conditions[53].



(24), R = H; *(25)*, R = Ac;
(26), R = *n*-C_3H_7CO

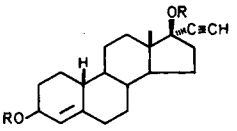


(27)

n-Butyl 11β-acetoxy-6α-fluoro-16α-methyl-3,20-dioxo-1,4-pregnadien-21-ate (25):

To a solution of the ester *(24)* (2.0 g, 0.45 mmol) in 30 ml pyridine and 5 ml acetic anhydride is added DMAP (0.1 g, 0.8 mmol) and the mixture is allowed to stand overnight at room temperature. The reaction product is precipitated with ice water and taken up in dichloromethane. The solution is washed several times with water, dried over $MgSO_4$, and the residue remaining after evaporation is chromatographed on silica gel [eluent: *n*-hexane with 17–21 % acetone]. Recrystallization from acetone/hexane yields 1.80 g (82 %) *(25)* m.p. 148.3 °C.

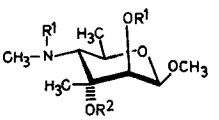
Of special interest is the esterification of tertiary 17β-OH groups in 17α-ethynyl steroids, since highly-active progestational agents are formed. The reaction, for example *(28)* → *(29)*, can be performed under mild conditions with acetic anhydride/DMAP/triethylamine (24 h, 24 °C)[56].



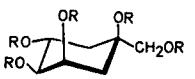
(28), R = H
(29), R = Ac

The DMAP-catalyzed acetylation of sterically-hindered hydroxyl groups has also been used to advantage in the total synthesis and acylation of natural products[46,49,57–59].

DMAP has also been employed as a catalyst for the acylation of sterically-hindered hydroxyl groups in carbohydrates. The reaction of methyl sibirosaminide *(30)* with acetic anhydride/pyridine yields only the *N*-acetyl acetate *(31)* whereas with acetic anhydride/DMAP/triethylamine the *N*-acetyl diacetate *(32)* is smoothly formed[60]. When treated with acetic anhydride/pyridine at room temperature (−)-*(33)* yields a mixture of products; however, after addition of DMAP the pentaacetate *(34)* is formed[61].

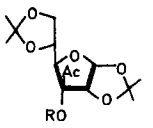


(30), $R^1 = R^2 = H$
(31), R^1 = Ac, R^2 = H
(32) $R^1 = R^2$ = Ac

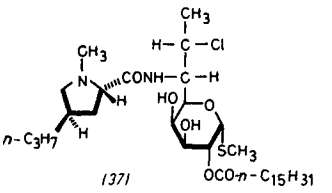


(33), R = H
(34), R = Ac

Paulsen et al.[62] were able to benzoylate the tertiary hydroxyl group in the furanose derivative *(35)* with benzoyl chloride, pyridine, and DMAP. The benzoyl moiety was then reductively removed from *(36)* with tri-*n*-butyltin hydride.



(35), R = H
(36), R = C_6H_5CO



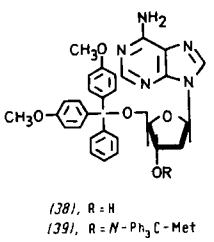
(37)

3-C-Acetyl-3-O-benzoyl-1,2:5,6-di-O-isopropyliden-α-D-allofuranose (36):

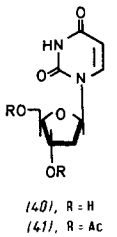
The sugar derivative *(35)* (0.39 g, 1 mmol) in 5 ml anhydrous pyridine is treated with 2 ml benzoyl chloride and DMAP (100 mg, 0.8 mmol) at 0 °C. After allowing to stand for 2 days at 24 °C, the mixture is diluted with 10 ml acetone/water (1:1), and solid $NaHCO_3$ is added until saturation is obtained. After 1 h, the solution is evaporated *in vacuo*. The residue is taken up in chloroform and the resulting solution is washed twice with water, then with 1 N H_2SO_4 followed by saturated $NaHCO_3$ solution, and finally with water. The chloroform layers are dried over $MgSO_4$ and evaporated *in vacuo*. The oil thus obtained is dissolved in $CHCl_3$/*n*-hexane (1:1) and stirred for *ca.* 30 min with 1 g silica gel. After filtration, *(36)* is crystallized from *n*-hexane at −20 °C; yield: 0.34 g (85 %), m.p. 107 °C; $[\alpha]_D^{20} = +120°$ ($c = 1.0$ in $CHCl_3$).

The enormous increase in acylation rates and the quantitative conversions obtained with DMAP or PPY as catalysts make their use attractive also for acylations of unhindered primary and secondary alcohols. *Connors* and *Albert*[63] recommend the use of the acetic anhydride/DMAP/pyridine reagent for the quantitative determination of hydroxyl groups in alcohols and phenols. The rate of acetylation of isopropanol at 54 °C is increased by a factor of 2×10^4 when pyridine is replaced by DMAP. Clindamycin palmitate *(37)* can be quantitatively acetylated with DMAP catalysis within 30 min at 24 °C whereas the same transformation in pyridine requires 3 h at 95 °C[64].

It is also possible with the aid of DMAP to fix Boc-amino acids on hydroxymethyl resins for the solid phase synthesis of peptides[65–67]. *Robins et al.*[68] have used catalytic quantities of DMAP to effect acylation of 2′-deoxyadenosine derivatives *(38)* with the symmetrical anhydride generated from *N*-trityl-L-methionine and dicyclohexylcarbodiimide *in situ*.



(38), R = H
(39), R = *N*-Ph_3C-Met



(40), R = H
(41), R = Ac

In pyridine alone, no trace of the product *(39)* could be detected. In the acylation of *(40)* to *(41)*, the use of DMAP as catalyst prevents the formation of colored side products and a diacetate of such purity (yield >90 %) is obtained that further purification by chromatography is no longer necessary[69].

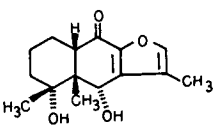
Generally, the esterification of carboxylic acids with alcohols and thiols with the aid of dicyclohexylcarbodiimide in the presence of catalytic quantities of DMAP proceeds in high yields. Thus, methyl 2,4,6-trimethylbenzoate is obtained in 74% yield, di-*tert*-butyl malonate in 86% yield, and *S*-ethyl thiopropionate in 85% yield[70].

Dicarboxylic anhydrides react with alcohols in the presence of DMAP or PPY catalysis to form the half esters, which can be used, for example, for the resolution of racemates[1, 71].

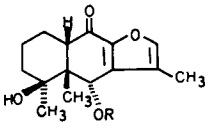
Mono-(−)-menthyl phthalate

A solution of (−)-menthol (3.1 g, 20 mmol), phthalic acid anhydride (6.0 g, 34 mmol), triethylamine (4.1 ml, 30 mmol), and DMAP (0.5 g, 4.1 mmol) in 20 ml dioxane is allowed to stand for 6 h at 24 °C. After dilution with ether, the mixture is extracted with 2 N HCl and the organic layer is dried over $MgSO_4$. After evaporation of excess solvent, the oily residue is dissolved in CCl_4 and separated from the phthalic acid present by filtration. After evaporation and drying *in vacuo*, 5.6 g (92%) of the half ester, m.p. 90—93 °C, is obtained; after recrystallization from methanol/water, m.p. 111 °C, $[\alpha]_D^{20} = 89.2°$ ($c = 5$ in $CHCl_3$).

Whereas *tert*-butyl alcohol can be esterified with isobutyric anhydride in the presence of DMAP as catalyst, reaction of the same alcohol with pivalic anhydride does not take place[1]. The limits of this method also become evident on attempted esterification of the sterically-hindered sesquiterpene diols *(42)* and *(43)*: in the case of *(43)* it is possible



(42)

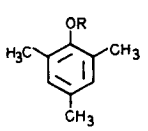


(43), R = H
(44), R = Ac

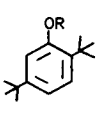
to acylate only the secondary hydroxyl group with acetic anhydride/DMAP, while *(42)* remains unchanged as a result of the strong hydrogen bond between the OH groups[72].

4.2. Acylation of Phenols

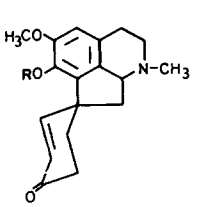
In the acylation of phenols, DMAP and PPY effect a similar increase in reaction rate as is found in the case of alcohols. Hence, the method is of interest for the acylation of sterically hindered phenols. For example, mesitol *(45)* can be smoothly acetylated with acetic anhydride/DMAP to *(46)*[1] and 2,5-di-*tert*-butylphenol *(47)* and analogous compounds can be transformed into acyl derivatives of the type *(48)* in high yields[73]. 11,12-Dihydroglaziovine *(49)* smoothly affords the acyl derivative *(50)*[74].



(45), R = H
(46), R = Ac

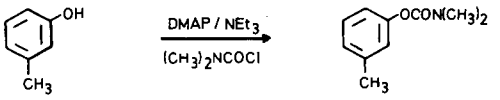


(47), R = H
(48), R = COCOCl



(49), R = H
(50), R = Ac

m-Cresol, dimethylcarbamoyl chloride, and triethylamine remain unchanged even after 2 hours' heating under reflux in tetrahydrofuran. Addition of 2 mmol DMAP to 100 mmol reaction mixture under the same conditions effects quantitative conversion into the dimethylcarbamate *(51)*[75].



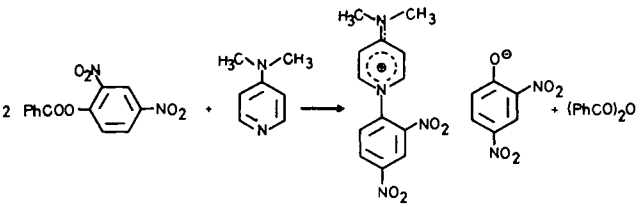
(51)

As mentioned in Section 4.1, phenols can be analytically determined with the aid of acetic anhydride/DMAP/pyridine[63].

4.3. Acylation of Amines

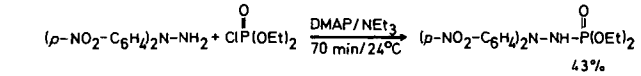
DMAP and PPY have been seldom used for the acylation of amines. The kinetic investigations of *Litvinenko* and *Kirichenko*[6] have shown that an enormous increase in reaction rate is observed when acylations are carried out in aprotic solvents. These authors have determined the following relative rate constants (in parentheses) for the amine-catalyzed acylation of *m*-chloroaniline with benzoyl chloride in benzene: *N*,*N*-dimethylaniline (0.1); triethylamine (0.072); 2,6-dimethylpyridine (0.03); pyridine (1.80); 4-methylpyridine (10.0); and DMAP (10600).

According to investigations by *Pietta* and *Brenna*[76], acetic anhydride/DMAP in dichloromethane could possibly be suitable for blocking unreacted amino groups on Merrifield resins. Attempts to increase the rate of reaction of *N*-(benzoyloxycarbonyl)valine *p*-nitrophenyl ester with valine methyl ester remained unsuccessful[77]. The more strongly activated 2,4-dinitrophenyl benzoate is attacked by DMAP (as a nucleophile) at the aromatic ring to form the pyridinium salt *(52)* and benzoic anhydride[78].



(52)

A catalytic effect of DMAP was observed in the phosphorylation of 1,1-bis(*p*-nitrophenyl)hydrazine *(53)*. When *(53)* is allowed to react with diethyl chlorophosphate *(54)* in the presence of DMAP, the desired hydrazine derivative *(55)* is formed. When pyridine or triethylamine is used, no reaction is observed[79].

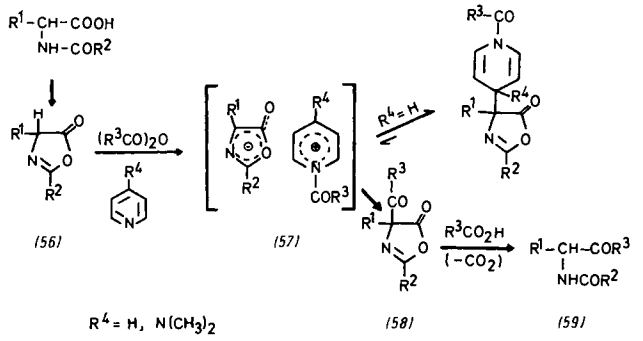


(53) *(54)* *(55)* 43%

4.4. Acylation of Enolates

Acylations involving CH-acid compounds which can be performed with pyridine or triethylamine as catalyst are found to proceed at a much higher rate when DMAP or PPY is

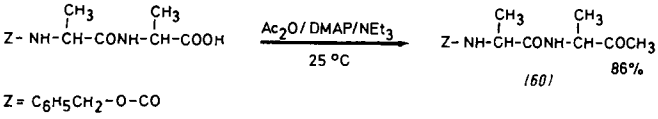
used. The Dakin-West reaction of *N*-acyl amino acids[80], in which a 2-oxazolin-5-one *(56)* is acetylated at C-4 with a carboxylic anhydride in pyridine with formation of a new C—C bond to give *(58)*, has been extensively investigated[81–83]. The combination products, consisting of the ambident oxazolin-5-one anions and *N*-acylpyridinium cations initially formed under kinetic control, are transformed *via* the ion pair *(57)* into the thermodynamically most stable product *(58)*[84,85]. Decarboxylative ring opening by the subsequently formed carboxylic acid yields the α-acyl amino ketone *(59)*[83,86,87].



(56) *(57)* *(58)* *(59)*

In the presence of DMAP or DMAP/NEt_3, this transformation can be carried out at room temperature or with gentle warming[7,88,89]. Normally, much higher temperatures and longer reaction times are required. It is therefore possible to avoid side reactions and to convert even sensitive amino acids such as tryptophan into α-acyl amino ketones in good yields.

These mild reaction conditions permit the exchange of a carboxyl group for an acyl group in *N*-protected peptides; for example, as in *(60)*[89].



(60)

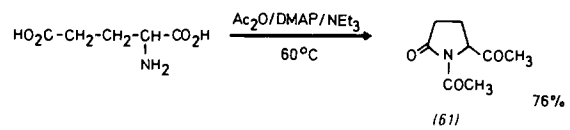
This method can obviously be used for the determination of C-terminal amino acids in peptides[90].

3-(N-Benzyloxycarbonylalanylamino)-2-butanone (60):

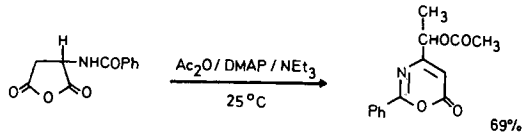
To *N*-benzyloxycarbonylalanylalanine (1.47 g, 5 mmol) in acetic anhydride (1.53 g, 15 mmol) and triethylamine (1.01 g, 10 mmol) is added DMAP (0.05 g, 0.4 mmol). After evolution of CO_2 has subsided, the mixture is treated with 20 ml methanol[*] and evaporated *in vacuo*. The residue is dissolved in ethyl acetate and the resulting solution is washed successively with 1 N HCl, aqueous $NaHCO_3$ solution, and water. After evaporation of excess solvent *in vacuo*, there remains 1.20 g (86%) *(60)*, m.p. 119 °C (recrystallized from ethyl acetate/petroleum ether).

In some cases the acyl amino ketones formed from the amino acids undergo further reactions. Thus, glutamic acid is found to yield 1,5-diacetyl-2-pyrrolidone *(61)*, and *N*-benzoylaspartic anhydride *(62)* the 1,3-oxazinone *(63)*[88].

[*] DMAP catalyzes the removal of excess acetic anhydride by ester formation. The addition of 1—2 equivalents of methanol is also advisable in the isolation of other acetylation reaction products. Compare also the preparation of *(22)*.

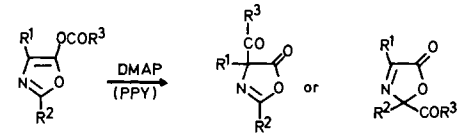


(61)



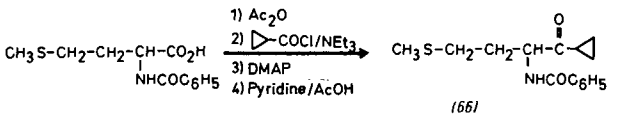
(62) *(63)*

Of preparative interest is the DMAP-catalyzed rearrangement of 5-acyloxyoxazoles *(64)* to 4-acyl-2-oxazolin-5-ones *(58)* or 2-acyl-3-oxazolin *(65)*[8].



(64) *(58)* *(65)*

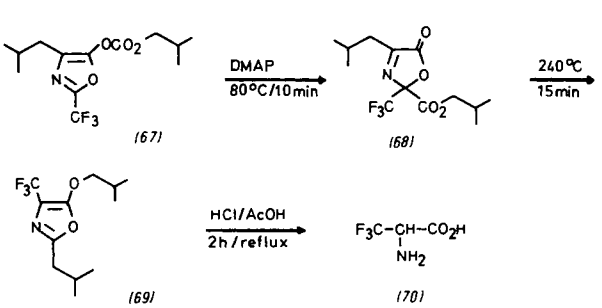
With pyridine, *(64)* (R^1 = *i*-Pr, R^2 = Ph, R^3 = Me) has to be heated for several hours at 100 °C to effect complete rearrangement, whereas addition of 5 mg DMAP is sufficient to complete the rearrangement of 100 mg of this oxazole within a few minutes (the reaction is very exothermic). When R^2 in *(64)* is an electron-withdrawing group, the acyl moiety is directed to the 2-position, allowing synthesis of compounds of the type *(65)*[8,92]. The rearrangement *(64)* → *(58)* can also be used to advantage when the Dakin-West reaction is performed with sensitive carboxylic acids. The *N*-acyl amino acid is transformed into the oxazolinone *(56)* which yields *(64)* upon treatment with R^3COCl/NEt_3[91]. After addition of a catalytic amount of DMAP or PPY, *(64)* rearranges to *(58)*, which on warming with oxalic or acetic acid in pyridine furnishes the α-acyl amino ketone *(59)*[91]. The intermediates do not have to be isolated. An example of this transformation is the synthesis of the α-acyl amino ketone *(66)* in 85% overall yield[93].



(66)

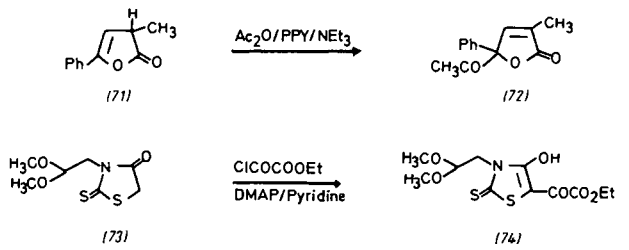
The DMAP-catalyzed rearrangement of the oxazole *(67)* to the 3-oxazolin-5-one *(68)* permits the effective synthesis of 3,3,3-trifluoroalanine *(70)*[92].

Further examples of *C*-acylation include the reaction of the furanone *(71)* with acetic anhydride/PPY/NEt_3 to give



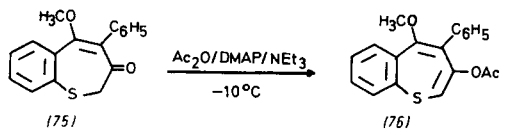
(67) *(68)* *(69)* *(70)*

the 5-acetyl derivative *(72)*[94] and the transformation of the rhodanin *(73)* into the 5-ethoxalyl derivative *(74)* with ethoxalyl chloride/DMAP/pyridine[95].



(71) *(72)* *(73)* *(74)*

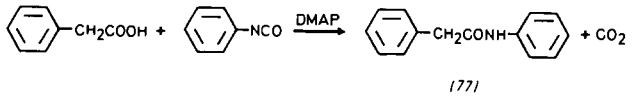
In some cases, the reaction of enolates with acetic anhydride/DMAP results in *O*-acylation. Thus, *Hofmann et al.*[96] were able to transform the bicyclic ketone *(75)* into the 1-benzothiepin derivative *(76)*.



(75) *(76)*

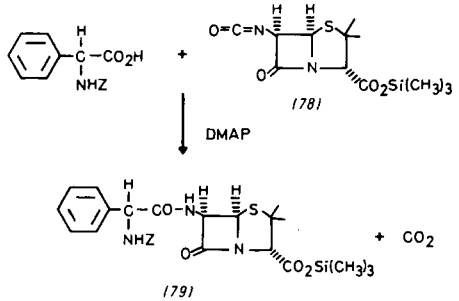
4.5. Reactions of Isocyanates

Pyridine-catalyzed reactions of isocyanates with carboxylic acids to form amides are found to be strongly accelerated on replacement of pyridine by DMAP. Phenylacetic acid is found to react with phenyl isocyanate in 1,2-dichloroethane at 24 °C to give the amide *(77)* in 66% yield in less than 5 min; whereas on using the same amount of pyridine only 53% *(77)* could be isolated after 2 h. With triethylamine, only very little *(77)* is formed besides diphenylurea[97, 98].



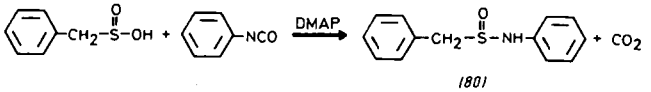
(77)

Similarly, reactions of trimethylsilyl 6-isocyanatopenicillanate *(78)* with, for example, D-*N*-benzoyloxycarbonyl-2-phenylglycine to give the ampicillin derivative *(79)*, are markedly accelerated by DMAP[97].



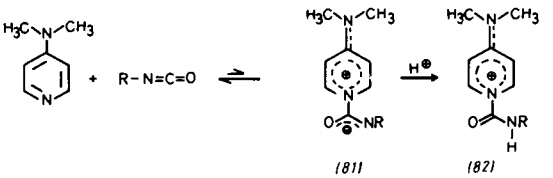
(78) *(79)*

Reaction of phenyl isocyanate or trimethylsilyl 7-isocyanatocephalosporanate with sulfinic acids in the presence of DMAP affords the sulfinamides, *e.g. (80)*, in high yields[99].



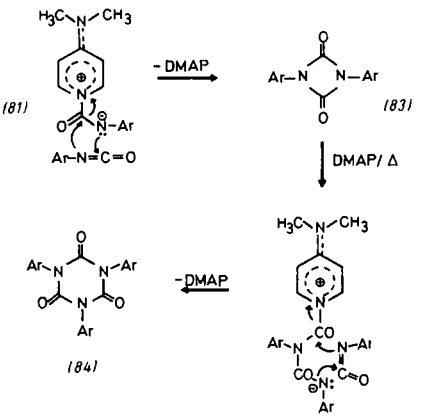
(80)

Since pyridine and triethylamine are poor catalysts for this transformation, it is assumed that DMAP and the isocyanate are in equilibrium with the dipole *(81)* which is converted by protonation into the more reactive *N*-carbamoylpyridinium ion *(82)*. *(82)* reacts readily with carboxylates, phenolates, and alkoxides (with loss of CO_2) to yield amides or urethanes.



(81) *(82)*

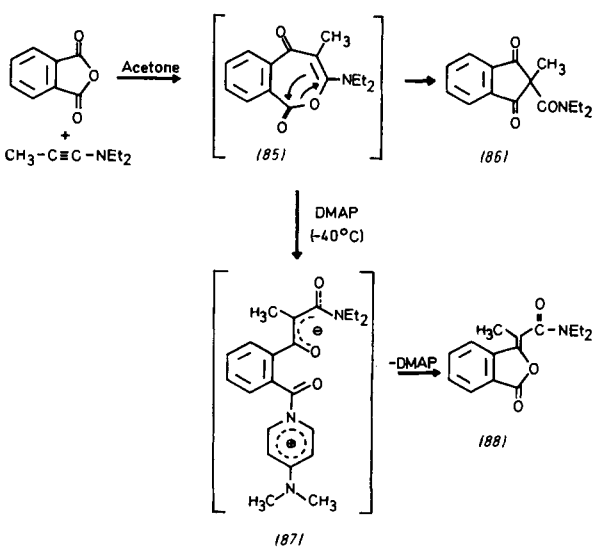
When no other reactant is present, the dipole *(81)*, R = Ar, reacts further with free aryl isocyanate in ethyl acetate to form the dimeric isocyanate *(83)*[100]. On heating, these 1,3-diazetidinediones are transformed into the more stable isocyanurates *(84)*.



(81) *(83)* *(84)*

In such dimerization and trimerization reactions, DMAP effects no increase in the rate of reaction, and the yields of products are not improved compared to those obtained in transformations with the usual catalysts such as 4-morpholinopyridine, 4-ethoxypyridine, or pyridine[101].

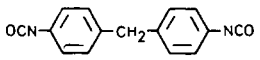
An interesting directive effect is observed in the reaction of phthalic anhydride with *N*,*N*-diethyl-1-propynylamine. Dipolar intermediates similar to those described above are



(85) *(86)* *(87)* *(88)*

also involved in this transformation[102]. Normally, the indandione *(86)* is formed, *via* intermediate formation of the vinylogous anhydride *(85)*. When 0.1 equivalents of DMAP are added, ring-opening of *(85)* takes place with formation of the dipole *(87)*, which is stabilized by exclusive recyclization to the phthalide *(88)*. With 30 equivalents of pyridine, *(86)* and *(88)* are formed in the ratio of 9:1.

DMAP catalyzes also the polymerization of isocyanates such as *(89)*[103]. In a similar manner, polyesters of adipic acid, ethylene glycol, and glycerol (still containing free hydroxyl groups) with 2-methyl-1,4-phenylene diisocyanate as additive can be prepared with DMAP catalysis[104]. Polymeric

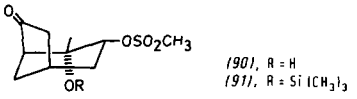


(89)

foams are obtained from phenols and polyisocyanates, especially 4-methyl- (or 2-methyl-)1,3-phenylene diisocyanates[105] and isophorone diisocyanate[106], with addition of DMAP.

4.6. Miscellaneous Applications

DMAP has been used in the hardening of epoxy resins with dicyanodiamine[107], in the transformation of nitriles into thioamides[108], and in the transfer of silyl groups to tertiary hydroxyl groups as shown by the conversion of *(90)* to *(91)*[109].



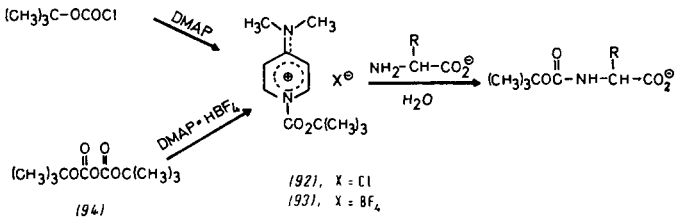
(90), R = H
(91), R = Si(CH$_3$)$_3$

5. Stable 4-Dimethylaminopyridinium Salts as Reagents for the Transfer of Functional Groups

In contrast to the behavior of *N*-acetyl-4-dimethylaminopyridinium ion in aprotic solvents, the hydrolysis of this salt in water proceeds approximately 2000 times slower than that of 1-acetylpyridinium ion[110] (see also Section 8.3). Dimethylaminopyridinium salts are therefore interesting reagents for the transfer of acyl and also cyano and phosphono groups in aqueous medium.

5.1. Transfer of Boc-groups

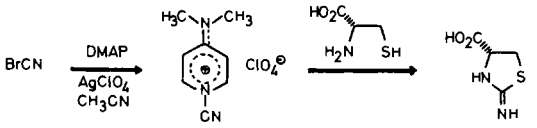
Wakselman and *Guibé-Jampel*[111] introduced 1-*tert*-butoxycarbonyl-4-dimethylaminopyridinium chloride *(92)* as a water-soluble reagent for the transfer of Boc-groups to amines and amino acids. *(92)* can be synthesized from DMAP and the labile butoxycarbonyl chloride in ether. The tetrafluoroborate *(93)* has proved to be more stable than *(92)* and can be prepared from the commercially-available di-*tert*-butyldicarbonate *(94)* and DMAP·HBF$_4$[112]. Both reagents lead to Boc-derivatives of amines and amino acids in aqueous solution.



(92), X = Cl
(93), X = BF$_4$
(94)

5.2. Transfer of Cyano Groups

The reaction of cyanogen bromide with DMAP and silver perchlorate yields the stable 1-cyano-4-dimethylaminopyridinium perchlorate *(95)*[113]. Further reaction of this salt with cysteine in aqueous solution gives the intermediate *S*-cyano compound which undergoes cyclization to the 2-iminothiazolidine-4-carboxylic acid *(96)* in quantitative yield. The salt *(95)* is also well suited for the transformation of SH groups in proteins.



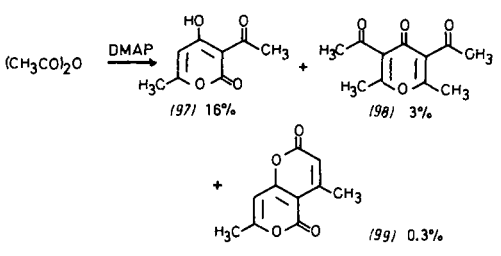
(95) *(96)*

5.3. Transfer of Phosphono Groups

Lawlor[114] and *Wakselman*[110] have prepared stable *N*-phosphono-4-dimethylaminopyridinium salts which, according to kinetic investigations[114], were capable of transferring the phosphono group to methylamine. A more detailed investigation would be worthwhile. (For the transfer of diethyl chlorophosphate *(54)* to amines in non-aqueous solution, see Section 4.3.)

6. Side Reactions

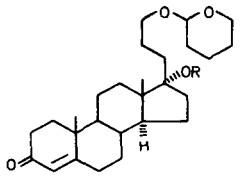
Acetic anhydride and DMAP in high concentrations can react to yield unwanted condensation products of acetic anhydride. Upon mixing equimolar quantities of DMAP and acetic anhydride the solution begins to boil spontaneously after a short induction period and becomes colored. Among the products formed are dehydracetic acid *(97)* as well as the condensation products *(98)* and *(99)*[115]. Self-acetylation of acetic anhydride has also been observed during the transformation of difficultly acylatable 17α-hydroxy steroids of type *(100)* with excess acetic anhydride and DMAP in pyridine[116].



(97) 16% *(98)* 3% *(99)* 0.3%

In addition to the expected acetate *(101)*, there are also formed the acetylacetate *(102)* and the (*E*)- and (*Z*)-enol acetates *(103)* derived therefrom[116].

Side reactions of this kind are undoubtedly exceptions which do not occur in dilute solutions. Reactions involving DMAP and PPY and acetic anhydride in high concentrations should therefore be avoided.



(100), R = H; *(101)*, R = Ac; *(102)*, R = $COCH_2COCH_3$
(103), R = $COCH=\underset{\displaystyle OAc}{\overset{\displaystyle |}{C}}-CH_3$

7. Toxicity of DMAP[117]

Table 2 shows the results of systemic tolerance studies of DMAP administered as a single dose in aqueous emulsion or solution.

Table 2. Toxicity data of DMAP.

Application	Animal	LD_{50} [mg/kg]	Confidence limits
oral	rat (M+F)	230	192—278
oral	mouse (F)	119	102—130
oral	mouse (M)	127	121—134
dermal	rat (M+F)	*ca.* 500 [a] 50 [b]	

[a] 5% (w/v) aqueous solution. [b] 12.5% (w/v) aqueous emulsion.

DMAP solutions or emulsions are found to cause serious changes when applied to intact and scarred rabbit skin which can lead to necrosis. The mucous membranes of rabbit eyes become strongly inflamed and burns appear. Contact of DMAP with the skin should therefore be avoided because of the danger of local and systemic effects. With DMAP salts (such as citrate), the dermal toxicity is reduced to such an extent that even high concentrations (12 g/100 ml) of this substance produce only a local irritation. In case of contamination of the skin with DMAP, it is advisable to wash the affected areas with dilute acids.

8. Mechanism of Acylation Reactions with 4-Dialkylaminopyridines

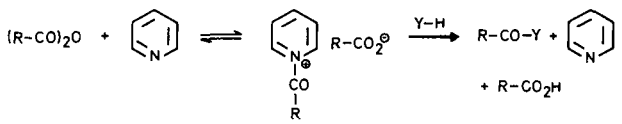
8.1. Introductory Remarks

For a discussion of the exceptional catalytic activity of the 4-dialkylaminopyridines, the role of bases in acyl-transfer reactions has to be discussed in more detail. Bases can assume three functions in this process:

1) As Brønsted bases B, they can produce an anion Y^- from a substrate H—Y. This anion is a better nucleophile than H—Y and therefore reacts more rapidly with the electrophilic acylating reagent. The extent of general base catalysis depends upon the relative basicities of B and Y^-, *i.e.* upon the position of the acid-base equilibrium

$$Y{-}H + B \rightleftharpoons Y^- + H{-}B^+$$

2) It has been found that in addition to attacking the substrate, nucleophilic and sterically unhindered bases are especially prone to attack the acylation reagent with formation of salt-like intermediates. For example, carboxylic anhydrides and pyridine yield small amounts of the *N*-acylpyridinium carboxylates *(104)*[118,119] which, because of their charge, are more capable of transferring an acyl residue to a nucleophile than the anhydride itself. Even acyl halides react slower with nucleophiles than *(104)*.



(104)

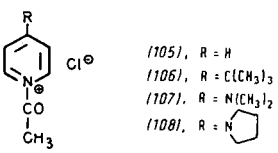
The extent of this nucleophilic catalysis[120] depends on the reactivity and concentration of the acylium salts which is, in turn, determined by the position of the equilibrium.

3) The third function of the base lies in the neutralization of acid generated during the reaction. To maintain the catalytic effect until complete conversion into product has been attained, it is necessary to use one equivalent of base for this purpose.

On comparing the basicity of pyridine ($pK_a = 5.29$) with that of DMAP ($pK_a = 9.70$), it could be surmised that the increase in reactivity of DMAP is due to the 2.6×10^4-fold increase in basicity. That this is not the case is shown by triethylamine ($pK_a = 10.65$) which is about as active as pyridine. Hence, the only possible reason for the increase in activity is the increased nucleophilic catalysis.

8.2. Formation of *N*-Acylpyridinium Salts

Reaction of pyridine with acyl chlorides usually furnishes the crystalline *N*-acylpyridinium halides[121] such as *(105)* in quantitative yields under mild conditions. These substances are also highly activated acid derivatives.



(105), R = H
(106), R = $C(CH_3)_3$
(107), R = $N(CH_3)_2$
(108), R = N⬠

These salts are of little use for preparative acylations, being insoluble in aprotic solvents[*]. However, a *tert*-butyl substituent on the pyridine ring increases the solubility to such an extent that the NMR spectrum of *(106)* can be investigated at −75 °C[23] (Fig. 1). As expected, acetyl chloride reacts with DMAP and PPY to form the salts *(107)*[110] and *(108)*[23], respectively, which are readily soluble in DMSO but less soluble in $CDCl_3$.

While examining the acetic anhydride/pyridine system several years ago, *Fersht* and *Jencks*[119] proved the existence of *N*-acetylpyridinium acetate *(104)*, R = CH_3, in aqueous solution by UV spectroscopy. However, in aprotic solvents, *i.e.* in those solutions in which acylation reactions are generally

[*] When pure *(105)* is suspended in $CDCl_3$, a *ca.* 0.5 mol/l solution is formed which is shown by its NMR spectrum to consist of a mixture of pyridine and acetyl chloride[23] ($\delta_{CH_3} = 2.68$).

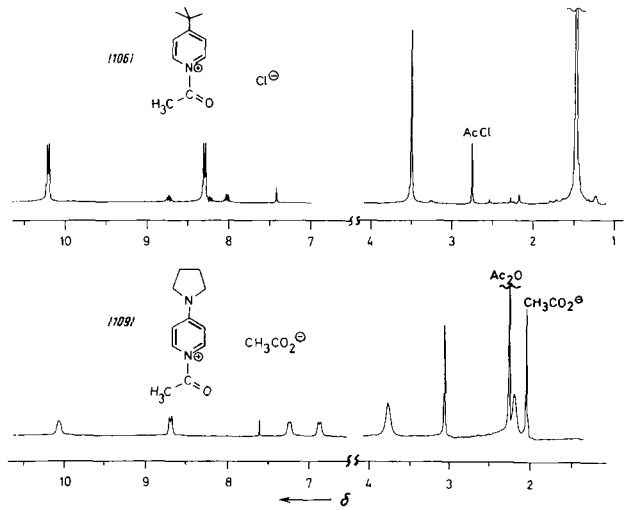
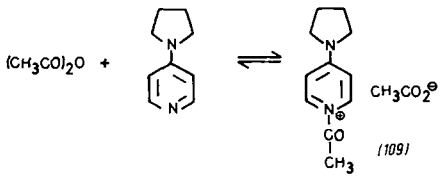
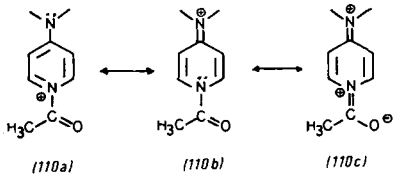


Fig. 1. ^{1}H-NMR spectra of 1-acetyl-4-*tert*-butylpyridinium chloride *(106)* (0.75 mol/l in $CDCl_3$) at −75 °C and 1-acetyl-4-pyrrolidinopyridinium acetate *(109)* (from 0.3 mol/l PPY and 0.45 mol/l acetic anhydride) in $CDCl_3/CD_2Cl_2$ (1:1) at −115 °C. Measurements made with Bruker WH-270 instrument at 270 MHz and −70 to −115 °C. The temperature dependence of the equilibrium concentration of *(109)* was determined in each instance with 0.1 M solutions of PPY and acetic anhydride in $CDCl_3$.

carried out, the existence of *N*-acetylpyridinium acetate could not yet be demonstrated[122] and its occurrence in these solvents has been seriously doubted[123]. In mixtures of acetic anhydride and DMAP or PPY appreciable quantities of *N*-acetyl-4-dialkylaminopyridinium acetate *(109)* can be detected, even in such solvents as $CDCl_3$ and CD_2Cl_2, provided that the exchange of acetyl with anhydride is sufficiently suppressed by lowering the temperature[23].



From the position of the equilibrium [50% *(109)* at −70 °C and 80% at −100 °C], it can be estimated that *(109)* is *ca.* 25 kJ/mol lower in energy than the starting materials and that 5—10% of *(109)* must be present at room temperature. PPY is converted completely into *(109)* with 1.5 equivalents of acetic anhydride at −115 °C[23] (Fig. 1). This extraordinary shift in equilibrium (when compared with pyridine) is caused by the gain in energy due to the mesomeric stabilization of the *N*-acyl-4-dialkylaminopyridinium ion *(110)*.



That the mesomeric form *(110c)* also contributes considerably to the stabilization of this anion has been shown by the NMR spectrum. Two sets of signals are observed for the α- and β-protons of the pyridine nucleus which arise from restricted rotation (at very low energy) around the acetyl-nitrogen bond (Fig. 1)[23].

An indication of the charge distribution can be obtained by the position of the acetyl-methyl signals. In compound *(106)*, where the positive charge is largely localized on the nitrogen, $\delta = 3.53$, whereas with 4-dialkylaminopyridinium salts *(109)* $\delta = 3.05$ and *(107)* $\delta = 3.04$ in $CDCl_3$[23]. Solvation with DMSO leads to a signal shift in compound *(107)* to $\delta = 2.82$[110]. The same tendency is found for the IR carbonyl frequencies which appear at 1800 cm^{-1} for compounds *(105)*[121] and *(106)*[23] and at 1755 cm^{-1} for *(107)*. The increase in the equilibrium concentration of acylpyridinium ions on introduction of a 4-dialkylamino group is accompanied by a pronounced reduction of the carbonyl activation.

8.3. Reactivity of *N*-Acylpyridinium Salts

Table 3 summarizes the results of acetylation of 1-ethynylcyclohexanol *(13)* with various acetylation reagents and catalysts in $CDCl_3$, a nonpolar solvent system[23].

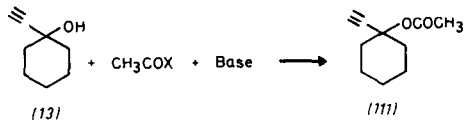


Table 3. Rate of acetylation of 1-ethynylcyclohexanol *(13)* (0.2 mol/l) with acetic anhydride or acetyl chloride (each in concentration of 0.4 mol/l) in the presence of various bases (catalysts) in $CDCl_3$ at 27 °C. The reactions were monitored by NMR spectroscopy (270 MHz, Bruker WH-270); the conversion was measured by integration of the signals of the acetylene protons in *(13)* ($\delta = 2.48$) and *(111)* ($\delta = 2.60$).

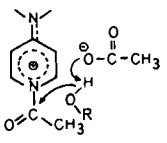
Run	Base	*c* [mol/l]	Acetylation reagent	$\tau_{1/2}$ [min] [a]
1	PPY	0.6	$(CH_3CO)_2O$	3
2	DMAP	0.6		7
3	Pyridine	0.6		1000
4	Pyridine	0.6		1000
	NEt_3	0.6		
5	DMAP	0.6	CH_3COCl	20 [b]
6	*tert*-Butylpyridine	0.6		60 [b]
7	*tert*-Butylpyridine	0.6		40 [b]
	NEt_3	0.4		

[a] The rate was determined as the time required for 50% conversion into *(111)* ($\tau_{1/2}$; error ±10%).
[b] Formation of side products.

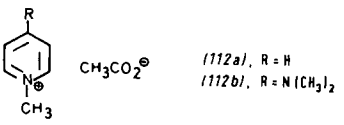
Runs 1—4 demonstrate once again the enormous catalytic activity of DMAP and PPY. PPY is, in this instance, *ca.* twice as active as DMAP (see [8,47]). Surprisingly, acylations with acetyl chloride (runs 5 and 6) are found to proceed much more slowly than those with acetic anhydride. The rate of acylation with acetyl chloride appears even more unfavorable when it is considered that only 5—10% of the acetylating species [for example *(109)*] is present at equilibrium in the case of acetic anhydride (see Section 8.2) when compared to 100% of *(107)* in the case of acetyl chloride. Varying amounts of free base have no significant effect on the reaction rate (run 7).

It can be deduced from Table 3 that in nonpolar solvents the rate of acyl transfer from *N*-acylpyridinium salts depends less upon the activation of the carbonyl group than upon the structure of the ion pair. According to our concept, an

increased mesomeric stabilization of the cation and anion leads to an increased expansion of the ion pair which, in turn facilitates attack of an external nucleophile. The *N*-acetylpyridinium chlorides *(105)* and *(106)* are very tightly bound ion pairs and therefore, in spite of the high degree of carbonyl activation, react very slowly. In *N*-acetyl-4-pyrrolidinopyridinium acetate *(109)*, the deactivation of the carbonyl group is more than compensated by the greater availability of the cation in the ion pair. At the same time, the acetate ion (which is always in the vicinity of the cation) can cause an increase in reaction rate by abstracting a proton from the nucleophile (general base catalysis)[124].



An indication of the greater ion mobility in pyridinium salts is provided by measurements of the specific conductivity. In 0.1 M solution in CH_2Cl_2 $\varkappa = 11.5 \times 10^{-3}$ for compound *(112a)*, and $56 \times 10^{-3}\ \Omega^{-1}\ cm^{-1}$ for *(112b)*[*].



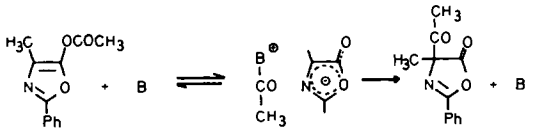
(112a), R = H
(112b), R = $N(CH_3)_2$

As expected, the degree of solvation has a strong effect on the reactivity of *N*-acylpyridinium salts. Experience has shown that acylation with DMAP or PPY proceeds best in non-polar solvents and this effect has been confirmed by comparing the acetylation of 1,1-diphenylethanol in various solvents: 75% acetylation occurred within 24 h in carbon tetrachloride or hexane, only 30% in methylene chloride or ether, and no reaction was observed in acetonitrile, nitromethane, or dimethylformamide[47].

Acylation proceeds even more slowly in protic solvents such as ethanol and especially in water. *N*-Acetyl-4-dimethylaminopyridinium chloride *(107)* hydrolyzes *ca.* 2000 times slower than the pyridinium salt *(105)* in acetate buffer solution at pH = 5.5[110]. Similar differences were observed with the *N*-phosphonopyridinium salts derived from γ-picoline and DMAP[114].

This reversal of reactivity in aqueous medium is understandable in view of the fact that the ion pairs do not react themselves but only the dissociated and solvated *N*-acylpyridinium ions. These then exhibit their "true" reactivity expected from their mesomeric stabilization and spectrochemical properties.

A comparison of the nucleophilic catalysis of several bases without interference from solvent effects and general base catalysis can be performed by studying the intramolecular acyl shift of 5-acyloxyoxazoles such as *(113)*. This transformation is catalyzed by many bases B to yield initially the ion pair *(114)* as intermediate which then rearranges to form the oxazolone *(115)*[8, 23, 91] [see *(64)* → *(58)* in Section 4.4].



(113) *(114)* *(115)*

In Figure 2, the reaction rates in benzene are plotted *versus* the pK_a value of the various bases. In the 4-substituted pyridine series, a linear free energy relationship is observed in which PPY exhibits the greatest activity. Because a further increase in the basicity of the pyridine system is hardly possible, it is unlikely that a better acyl transfer reagent than PPY will be found. 4-(Tetramethyl-2-guanidino)pyridine *(116)* is 90% as active as PPY for the acylation of alcohols[47].

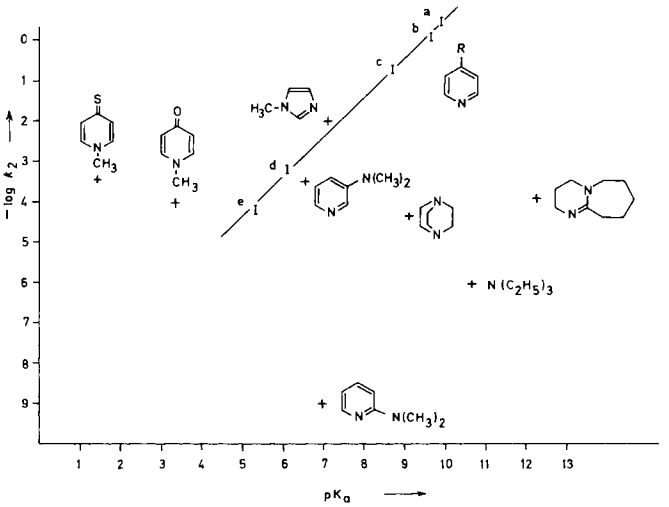
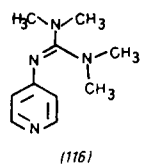
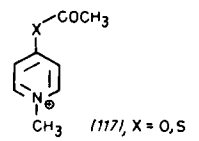


Fig. 2. Rate of the base-catalyzed rearrangement of *(113)* to *(115)* as a function of the dissociation constant of the base. The rearrangements were performed in benzene with 0.75 M solutions at 35°C with 1.5×10^{-3} to 0.35 mol/l of base and were monitored by NMR spectroscopy. The rate constants were first order and proportional to the concentration of the base. R in the 4-substituted pyridine-derivatives stands for: a, pyrrolidino (=PPY); b, $N(CH_3)_2$ (=DMAP); c, morpholino; d, CH_3; e, H.

N-Methylimidazole, a reagent which is also utilized[8] for this rearrangement, is *ca.* twice as active as a pyridine derivative with the same basicity. This is due to the smaller hindrance of the nucleophilic nitrogens by the α-protons. When the nucleophilic center is hindered by substitution, very small rearrangement rates are observed in spite of very high basicity,



(116)



(117), X = O, S

for example with 2-dimethylaminopyridine, triethylamine, and diazabicyclo[5.4.0]undecene (DBU). Diazabicyclo[2.2.0]octane, which has been recommended for use as an acylation catalyst[125], is as effective as pyridine because of the advantagous steric construction ("e" in Figure 2).

[*] *G. Höfle, B. Lange, H. Vorbrüggen*, unpublished; the conductivities were measured at 20°C in anhydrous CH_2Cl_2. Solutions of acetic anhydride (0.8 mol/l) and DMAP or pyridine (0.1 mol/l) exhibited specific conductivities of 1.4×10^{-3} and $1.6 \times 10^{-5}\ \Omega^{-1}\ cm^{-1}$. These results indicate that 2.5% of the DMAP is present as a salt *(112b)*. The poor conductivity of pyridine systems can be due to *(104)* as well as hydrolysis products.

Remarkably high rates of rearrangement are observed with relatively weak bases such as *N*-methyl-4-pyridone and *N*-methyl-4-thiopyridone, which form the activated 4-acyloxy- or 4-acylthiopyridinium salts *(117)* as intermediates. These bases are exceptions as the nucleophilic centers (oxygen and sulfur) are subject to negligible steric hindrance. They might conceivably be used for acylations in weakly acid solution.

In summary, two factors are responsible for the high activity of DMAP and PPY as acylation catalysts in aprotic, nonpolar solvents:

1) As a result of their pronounced nucleophilicities, these bases form high concentrations of *N*-acylpyridinium salts from acylation reagents even in nonpolar solvents. DMAP and PPY are far superior to pyridine and other amines in this respect.

2) Because of charge delocalization, the *N*-acyl-4-dialkylaminopyridinium salts are present as loosely-bound ion pairs, thus greatly facilitating attack of nucleophile on the activated acyl group with general base catalysis by the neighboring anion. This effect also explains why carboxylic anhydrides are better suited for these acylations than the corresponding acyl chlorides.

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Histidine in Enzyme Active Centers

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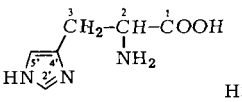
Dedicated to Professor Peter Karlson on the occasion of his 60th birthday

The presence of histidine in the active center of an enzyme can be demonstrated by kinetic measurements, chemical modification, NMR spectroscopy or X-ray structure analysis. Histidine is the only naturally occurring amino acid to contain an imidazole residue as a side chain. The role of histidine in enzyme catalysis depends, *inter alia*, upon the special features of the imidazole residue: it thus tends to form hydrogen bonds, combines donor and acceptor properties and can take part in either nucleophilic or base catalysis. In some of these enzymes the position of each atom is known; however, the theories as to how the catalysis proceeds at a molecular level are controversial.

1. Introduction

The amino acid histidine was isolated simultaneously in 1896 by *Kossel*[1] from sturine (a sturgeon sperm protein) and by *Hedin*[2] from several protein hydrolyzates (including those of casein and ovalbumin). *Pauly*[3] succeeded in elucidating the structure of histidine which was then finally proved in 1904 by *Knoop* and *Windaus*[4]. *Best et al.*[5] found that histamine, which had already been synthesized in 1907 by *Windaus* and *Vogt*[6], was by far the most important metabolic product of histidine.

Scientists were then mainly concerned with the histidine contents of proteins, especially with regard to their nutritional



Histidine

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physiology. The function of histidine in proteins, particularly in enzymes, first became of major interest at the beginning of the nineteen fifties when the concept of enzyme active centers had been firmly established[7]. Model reactions[8,9] were of valuable assistance to enzymologists and protein chemists in their efforts to elucidate the role of histidine in enzyme catalysis. A prerequisite for this work was, primarily, the development of specific methods for the identification of histidine in the active center. Well-founded proposals for the possible functions of histidine in enzyme catalysis could, however, only be made after the exact chemical, physicochemical and catalytic properties of imidazole were known.

2. Properties of Imidazole

2.1. Chemical and Physicochemical Properties

Imidazole (Im) is a flat heterocyclic molecule with six π electrons[10]; it has a resonance energy of 15.4 kcal/mol[11]. It is structurally related to both pyridine and pyrrole (resonance energies 20.9 and 8.5 kcal/mol, respectively). The aromatic cations ImH^+ and ImM^+ are formed by acceptance of a proton or complex formation with a metal ion respectively. N-1 and N-3 are equivalent in the imidazolium ion ImH^+.



Im ImH^+ ImM^+

In aqueous solution a tautomeric equilibrium is established with the solvent by means of proton exchange. The predominant exchange reaction in acid solution is

$$ImH^+ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Im + H^+$$

and in alkaline solution

$$Im + H_2O \underset{k_4}{\overset{k_3}{\rightleftharpoons}} ImH^+ + OH^-$$

The back reactions are thermodynamically favored; they have rate constants which are typical of diffusion-controlled processes, namely $k_2 = 10^{10.2}$ and $k_4 = 10^{10.4}\,s^{-1}\,l\,mol^{-1}$[12]. Since the p$K$ value of imidazole is 7.0 and $k_1/k_2 = K_a = 10^{-7}$, k_1 can be calculated to be $10^{3.2}$ and k_3 to be $10^{3.4}\,s^{-1}$. The similarity between these two values is due to the fact that

$$K_a = 10^{-7} = \sqrt{K_w} = [H^+] = [OH^-]$$

Imidazole is thus an optimal catalyst and buffer in aqueous solutions close to the neutral point[12]. The slowest step in the exchange between the hydrogen bonded to the nitrogen atom and the solvent components in alkaline solution is the protonation of neutral imidazole by water (k_3).

The protonation can be accelerated by general acid catalysis. If the imidazolium ion acts as an acid, the reaction proceeds according to the equation

$$Im + ImH^+ \rightleftharpoons ImH^+ + Im$$

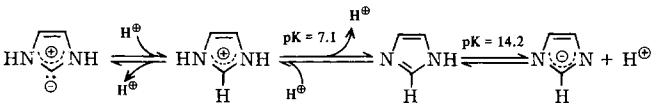
The rate constant for the forward and back reaction is approximately $10^{8.5}\,s^{-1}\,l\,mol^{-1}$.

Imidazole can be protonated not only at N-3 to give a cation ImH^+ (imidazolium ion; p$K = 7.1$; 25 °C, ionic strength 0.2), but can also be deprotonated in strongly alkaline solution at N-1 to give an anion (imidazolide ion; p$K = 14.2$ to 14.6)[13]. This anion, which is also aromatic, possesses two equivalent coordination sites and is thus a potent bond-forming ligand.

The formation of the ylide $Im^{\pm}$ by deprotonation of the imidazolium ion at C-2 must be mentioned, although in aqueous solution this is quantitatively of minor importance in the equilibrium. Exchange of the C-2 proton in D_2O proceeds rapidly; the half time of this reaction at 65 °C and pD = 6.9 is 10.9 min[14].



The protonation equilibria of imidazole can be summarized as follows:



$Im^{\pm}$ ImH^+ Im

Finally, the complex forming properties of imidazole must be mentioned[15]. In neutral solution unprotonated imidazole forms complexes using the free electron pair of N-3 (bonding with a metal at N-1 is very unlikely). Complex-bound imidazole can no longer participate in nucleophilic reactions since its nucleophilic center is required for the coordination of the metal ion. The aromatic character of imidazole is preserved in the formation of imidazole-metal complexes. The structure of the metal complexes and derivatives of imidazole together with those of histidine and histidine peptides cannot be dealt with here in more detail (for a review see[15]). The similarity between the binding constants of proteins and those of imidazole derivatives and histidine peptides led to the assumption that imidazole residues were involved in the binding of metals to proteins; more recently this assumption has been directly confirmed by X-ray structure analysis.

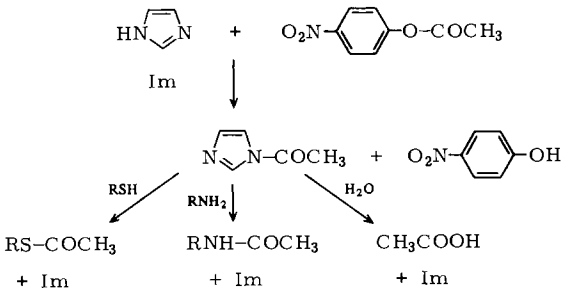
The fact that imidazole tends to form hydrogen bonds is one of its physicochemical properties which could be of importance for its role in enzyme catalysis[16]. The pyrrole nitrogen atom (N-1) tends to lose its protons whereas the pyridine nitrogen atom (N-3) can accept a proton. Donor and acceptor properties are thus combined in imidazole at pH values close to the neutral point! These features make imidazole an ideal substance for forming hydrogen bonds in biological systems, particularly in enzymes.

2.2. Catalytic Properties

Intensive study of the catalytic properties of imidazole began after *Hartley* and *Massey*[17] had observed that benzoyl histidine methyl ester catalyzed the hydrolysis of *p*-nitrophenyl acetate. Imidazole was thus the first organic base to be recognized as a catalyst of an ester hydrolysis. It was shown

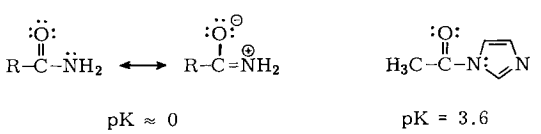
in numerous investigations that, depending on the structure of the ester, imidazole can take part in either nucleophilic or base catalysis.

Nucleophilic catalysis of ester hydrolysis was studied most thoroughly using the example of *p*-nitrophenyl acetate[18–22]; this is also an example for the catalysis of acyl transfer. Imidazole cannot displace strongly basic alcoholate ions from normal esters on account of its weak basic character; nucleophilic catalysis is therefore only observed during the hydrolysis of activated esters (anhydride character) which are derived from weakly basic alcoholates. Hydrolysis takes place with the intermediate formation of *N*-acetylimidazole, the decomposition of which is the slowest step in the entire reaction. In the presence of other nucleophilic agents such as SH compounds or amines, hydrolysis is replaced by acyl transfer—a reaction which is highly selective and which also takes place when there is a large excess of water[9, 19].



Imidazole has several properties which make it a particularly efficient nucleophilic catalyst[12]: it is a tertiary amine whose *N*-substituents are fixed in such a way that they are of only slight steric hindrance, this is because the nitrogen atom is a component of a five-membered, aromatic ring system. Imidazole's nucleophilic reactivity, which is higher than that of primary and secondary amines, can thus exert its full effect (in contrast to common tertiary amines). In addition imidazole, having a p*K* of 7, is the strongest base known at the neutral point (see Section 2.1).

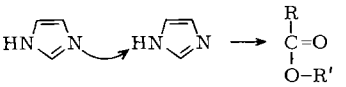
The intermediate *N*-acetylimidazole is much more reactive towards nucleophiles than normal amides on account of its low resonance stabilization. The lone electron pair of the nitrogen atom which can react with carbonyl groups in normal amides, is integrated within the π electron system of the imidazole in *N*-acetylimidazole and is thus not available.



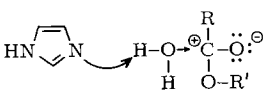
The basicity of acetylimidazole (p$K = 3.6$) is relatively high since a N atom other than the one which is acyl-substituted is protonated[23]. At the present time there is no convincing evidence that enzyme-bound imidazole acts as a nucleophilic catalyst in enzymatic acyl transfer reactions; in most biological acyl transfer reactions the substrates are not activated acyl compounds.

Some studies support the theory that imidazole can act as a nucleophilic catalyst in enzymes catalyzing the transfer of phosphate. *N*-Phosphonoimidazole has been identified as an intermediate in several enzymes (see Table 1). Using non-enzymatic model reactions, it was shown that imidazole is not a particularly good nucleophile towards monosubstituted phosphoric acid esters; under certain conditions, however, imidazole or phosphonoimidazole can catalyze the hydrolysis of phosphoric acid esters or phosphate transfer respectively[24–26]. Phosphonoimidazoles are approximately as reactive as other phosphoric acid amides.

As the basicity of the alcoholate in the ester increases, the nucleophilic catalysis of imidazole becomes less effective; ultimately, a second order dependence on the imidazole concentration is found in the rate equation which can be accounted for by a general base catalysis of the following type[27, 28]:



If the carbonyl carbon atom of the ester is positively polarized (as is the case, for example, with ethyl chloroacetate), imidazole acts as a general base catalyst in the hydrolysis of the ester; imidazole accepts a proton from a water molecule whose OH group then attacks the carbonyl carbon atom[29]:



Although an unequivocal model reaction utilizing imidazole as a general acid catalyst is not yet known, it is assumed that it can take part in general acid-base catalysis in enzymes.

General base catalysis of ester hydrolysis by imidazole requires the acceptance of a proton from a water molecule. Since the rate constant for proton transfer from a water molecule is $10^3\ s^{-1}$, the rate of this reaction should be the upper limit for hydrolytic, general base-catalyzed processes involving imidazole. Bases which are stronger than imidazole are protonated more rapidly but their conjugate acids are deprotonated more slowly than the imidazolium ion. In the case of a catalyst, protonation and deprotonation must follow one another; the rate of the catalyzed reaction is then determined by the slowest step. Imidazole is the most effective general base catalyst close to the neutral point for the reasons cited above. As the turnover numbers of hydrolytic enzymes are $10-15^5\ s^{-1}$ and the upper limit for catalysis involving imidazole is 10^3, it must be assumed that neighboring acidic or basic groups can enhance the rates of protonation and deprotonation. Turnover numbers in model experiments have been increased by factors of up to 100 by neighboring group effects[30]. Rate constants of up to $10^5\ s^{-1}$ are thus attained which correspond to those of the most efficient enzyme-catalyzed reactions. Rate constants of less than $10^3\ s^{-1}$ are found if other steps are rate limiting.

The importance of general acid-base catalysis for the action of enzymes is due to the fact that the same effect is obtained as that resulting from the intermediate formation of hydroxide or hydrogen ions. The base accepts a proton from the attacking water molecule and enhances the nucleophilic reactivity of the water without forming free hydroxide ions. In spite of this, general acid-base catalysis has only been demonstrated for a few enzymatic reactions (see Section 4).

3. Methods for the Identification of Histidine in Enzyme Active Centers

The question as to whether a certain amino acid is involved in the catalytic reaction of an enzyme or whether it is part of the active center can largely be investigated by the following methods:

1. kinetic measurements,
2. chemical modification and covalent labeling,
3. NMR spectroscopic measurements,
4. X-ray structure analysis.

3.1. Kinetic Measurements

Kinetic measurements of the pH dependence of enzyme activity can be used to determine the pK value of an amino acid essential for catalysis in favorable cases where the amino acid contains a dissociable group. Under certain conditions studies of the influence of pH on V_{max} and K_m also allow differentiation between groups which are directly involved in the catalysis and those which are primarily responsible for substrate binding[31]. In addition, the temperature dependence of the pH dependence can be utilized to obtain the dissociation energy of the functional group for which the pK has been determined. The pK value and dissociation energy can sometimes be assigned to a specific dissociable group essential for catalysis. It is obvious that kinetic measurements alone only permit identification of essential groups in favorable cases as, for example, the pK ranges of the functional groups of proteins overlap with one another to some extent and the information about their possible extreme values in enzymes is incomplete. Other factors give rise to apparent pK values which bear no relationship to those of the functional groups involved in the catalysis, this is particularly so with high and low pK values. The same considerations apply to the dissociation energies of functional groups within the protein.

pK values of between 5.6 and 7.0 are generally assumed for imidazole residues with dissociation energies of between 6.9 and 7.5 kcal/mol. The pK values of imidazole thus lie within a pH range in which protein denaturation scarcely ever occurs and where enzyme activity can usually be easily measured.

Nowadays it is not sufficient to assign the essential groups of an enzyme solely on the basis of kinetic measurements—a combination of several, independent experimental procedures has to be used.

3.2. Chemical Modification

The catalytic activities of enzymes in which individual amino acids have been chemically modified are now being investigated in many laboratories[32]. The modifying reagents should

1. have a specificity for a given amino acid which is as high as possible, and
2. react with the amino acid under the mildest conditions possible.

Although histidine's imidazole residue is, in principle, capable of undergoing numerous reactions (*e.g.* acylation, alkylation and electrophilic substitution), the number of suitable reactions for specific modification under mild conditions is small. Consultation of the literature shows that only a few reactions have found extensive application; of these reactions photooxidation must be mentioned first of all.

3.2.1. Chemical Modification by Photooxidation

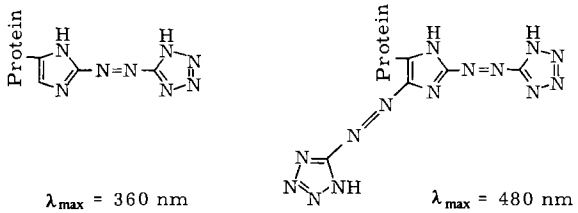
Photooxidation in the presence of methylene blue[33] or rose bengal[34] as sensitizers is used most frequently for the chemical modification of histidine residues in proteins. This procedure is gentle but still leaves something to be desired as far as specificity is concerned since tyrosine, tryptophan and cysteine can also be oxidized; the specificity depends to some extent on the pH of the reaction solution[35]. Histidine is thus especially sensitive to photooxidation in neutral solution in the presence of rose bengal. Its reaction products are aspartic acid and urea[36].

In order to obtain reliable information about the relationships between histidine oxidation and loss of enzyme activity, the pH dependence of the decrease in activity due to photooxidation should be included in the investigation and the tryptophan, tyrosine and methionine contents of the photooxidized protein should also be checked by amino acid analysis. Any methionine *S*-oxide formed can be reduced to methionine by SH compounds (*e.g.* thioglycollic acid, mercaptoethanol). After the reaction the dye is best removed by gel filtration, which, in the case of rose bengal, sometimes gives rise to difficulties. Complete removal of the dye by dialysis often takes a long time.

3.2.2. Chemical Modification by Azo Coupling

Pauly[3] had already observed in 1904 that histidine and tyrosine in proteins could couple with aromatic diazonium salts to give azo dyes. Since then this reaction has often been employed in immunology and enzymology to modify proteins; it takes place under mild conditions. The tetrazolediazonium ion introduced by *Horinishi* in 1964 is well suited[37,38]. It has the advantage that it does not form any colored side products which would increase the blank values in optical measurements. When histidine and tyrosine residues are coupled, mono- and bisazo compounds are produced, some of whose absorption maxima differ considerably and which under favorable conditions (not too much residue to be coupled, exclusive formation of the bisazo product) therefore permit the degree of modification to be determined spectroscopically; the absorption maxima of bis(tetrazolylazo)histidine and mono(tetrazolylazo)tyrosine are almost identical. It is thus highly desirable to check the degree of modification by amino acid analysis. The coupling rates of histidine and tyrosine residues with the tetrazolediazonium ion decrease drastically with decreasing pH.

Although valuable information about the essential histidine residues of enzymes can be gained from coupling experiments of this type, the fact that the specificity of this reaction is

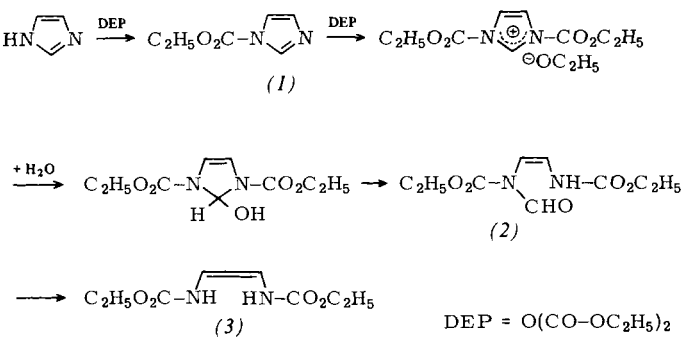


low must not be overlooked. In addition to histidine and tyrosine which form colored coupling products, amino groups, tryptophan and arginine also react and do so with a greater reactivity than histidine and tyrosine[39,40]. Under certain conditions the tetrazolediazonium ion is therefore also well suited for the modification of tryptophan[39]; the degree of modification of the tryptophan residues must be determined by amino acid analysis[41]. It should not be forgotten that the tetrazolediazonium ion is explosive and can only be synthesized from the amine in small quantities.

3.2.3. Chemical Modification by Diethyl Dicarbonate

As was shown in 1967[42], diethyl dicarbonate ("diethyl pyrocarbonate") (DEP) can be used under mild conditions as a reagent for modifying proteins with a considerable specificity for histidine. In addition to histidine, it can also react with tyrosine, tryptophan and amino groups[43]. DEP reacts with histidine at pH 4—7 to give N^{Im}-ethoxycarbonylhistidine *(1)* which has an absorption maximum at 240 nm that can be utilized for spectrophotometric measurements. The reaction is reversible: N^{Im}-ethoxycarbonylhistidine can, for example, be cleaved under mild conditions with hydroxylamine.

After difficulties arose with some enzymes in calculating the degree of modification from the published extinction coefficients for *(1)*[44,45], *Loosemore* and *Pratt* demonstrated in 1976[46] that the imidazole ring can also be cleaved under mild conditions in a subsequent, undesired reaction (Bamberger reaction). This reaction invalidates the spectrophotometric results as the spectra of *(1)*, *(2)* and *(3)* overlap one another. Amino acid analysis of the modified protein must therefore be performed to obtain the number of histidine residues destroyed. The precise conditions which favor quantitative ring cleavage of *(1)* in the protein molecule or which completely inhibit it are not known.



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

Spectrophotometric evaluation of the degree of modification at 240 nm is not possible if *(2)* and *(3)* are formed in significant quantities.

3.2.4. Chemical Modification by α-Halo Acetates, Chloromethyl Ketone and Iodine

In this section a few reagents will be mentioned which, in special cases, have given valuable information concerning the function of histidine in enzymatic reactions. Normally, α-halogen acetates only react very slowly with imidazole residues in proteins. In some enzymes, however, certain histidine residues show an unusually high reactivity which surpasses that of the imidazole in histidine itself[47–49]. High affinity of the modifying reagents for the enzyme active center containing the histidine residue is responsible for this exceptional reactivity. This is also the principle on which K_s inhibitors are based. The high specificities of these inhibitors are due to binding in the active center which follows a covalent reaction with a functional group[50]. Chloromethyl ketones, such as tosyllysylchloromethyl ketone[51] and tosylphenylalanylchloromethyl ketone[52] are K_s inhibitors which have been employed for the covalent labeling of the imidazole residues in the active centers of trypsin and chymotrypsin.

When interpreting alkylation experiments with α-halogen acetates and chloromethyl ketones, the fact that 1- and/or 3-substituted imidazoles and eventually 1,3-disubstituted imidazoles can be produced has to be taken into consideration. In the case of carboxymethyl derivatives the positional isomers can be identified by conventional amino acid analysis as the derivatives withstand acid hydrolysis.

As yet there are scarcely any examples of iodination being utilized to identify essential histidine residues[53]. Iodination of histidine gives 5′-iodo- and then 2′,5′-diiodohistidine[54,55] which are both destroyed by acid hydrolysis with the result that iodination can only be indirectly measured by amino acid analysis.

Histidine is only slightly more slowly iodinated than tyrosine. The ratio between tyrosine iodination and histidine iodination depends very strongly on the protein and conditions used[56]; it seems that the number of reacting histidines is often lower the higher the tryptophan content of the protein. At pH values >9, iodination of histidine is favored with respect to that of tyrosine; a pH optimum of 8.5 has been cited for tyrosine iodination.

3.3. NMR Spectroscopic Measurements

As is shown in Table 1, NMR spectroscopic measurements have yielded valuable information about the function and state of histidine residues in a series of enzymes. Although NMR spectroscopy gives reliable information about the structure and dynamic properties of low molecular weight compounds, the application of this technique to macromolecules and the interpretation of the results is not always simple[57]. First of all there must be adequate quantities of the compound and it should have a sufficiently high solubility in D_2O. The signals must be clearly separated from one another and it should be possible to assign them to known chemical groups within the system; furthermore, it should be possible to interpret the data with regard to the structure and dynamics of the system.

The ^{1}H-NMR signal of histidine's C-2′ proton is shifted by 1 ppm to a lower field strength by protonation of its imidazole nitrogen atom[58]. The pK values of the imidazole can then be determined by using the pH dependence of this shift. The pK values are influenced by interactions between imidazole and its neighboring groups, ions, substrates, inhibitors or other effectors. Conclusions about the rate of exchange between two or more states of the C-2′ proton can also be drawn from the changes in signal width. NMR measurements thus allow statements to be made about the alterations in the states of protein imidazole residues which accompany changes in the pH value.

Table 1. List of enzymes containing essential histidine residues and the methods used to identify the histidine.

No. (EC)	Enzyme	Method of detection [a]	Ref.
1.1.1.1	Alcohol dehydrogenase	DEP	[81]
1.1.1.30	D-3-Hydroxybutyrate dehydrogenase	DEP	[82]
1.1.1.37	Malate dehydrogenase	DEP	[83]
1.1.1.40	"Malic enzyme"	DEP	[84]
1.1.1.41	Isocitrate dehydrogenase	DEP, photoox. (M), alk. (α-Hal.)	[85]
1.1.1.64	Estradiol dehydrogenase	alk.	[86]
1.1.3.9	Galactose oxidase	alk. (α-Hal.)	[87]
1.4.3.2	L-Amino acid oxidase	kin., thermodyn.	[88]
1.4.3.4	Monoamine oxidase	DEP, photoox. (R), azo	[89]
1.5.1.11	Octopine dehydrogenase	photoox. (R)	[90]
1.13.12.4	Lactate 2-monooxygenase	DEP	[91]
1.15.1.1	Superoxide dismutase	$Br^{\bullet}$ (pulse radiolysis)	[92]
2.1.3.2	Aspartate transcarbamylase	photoox. (P), alk.	[93, 94]
2.2.1.2	Transaldolase	photoox. (R), [b]	[95, 96]
2.4.1.1	Phosphorylase	photoox. (R)	[97]
2.4.2.1	Purine nucleoside phosphorylase	kin.	[98]
2.6.1.1	Aspartate aminotransferase	photoox. (M), alk., kin.	[99]
2.7.1.11	6-Phosphofructo kinase	photoox. (M)	[100]
2.7.1.37	c-AMP-dependent histone kinase	[^{32}P]-P-His	[78, 101]
2.7.1.40	Pyruvate kinase	DEP	[102]
2.7.3.2	Kreatine kinase	DEP	[103]
2.7.3.3	Arginine kinase	DEP	[104]
2.7.4.3	Adenylate kinase	NMR	[105]
2.7.4.6	Nucleoside diphosphate kinase	kin.	[106]
		P-His	[107]
2.7.9.1	Pyruvate phosphate dikinase	[^{32}P]-P-His	[108]
3.1.1.3	Lipase	photoox., kin.	[109]
		DEP	[110]
3.1.1.4	Phospholipase A_2	alk. (*p*-bromoph.)	[111]
3.1.1.7	Acetylcholinesterase	kin.	[112]
3.1.3.1	Alkaline phosphatase	photoox. (M, R)	[113]
3.1.3.2	Acid phosphatase	photoox. (R)	[114]
		P-His	[115]
3.1.3.9	Glucose-6-phosphatase	kin.	[116, 117]
		P-His	[76]
3.1.4.3	Phospholipase C	DEP	[118]
3.1.4.5	Desoxyribonuclease	alk. (iodoacetate)	[119]
3.1.4.22	Ribonuclease (pancreas)	photoox.	[120]
		alk. (α-Hal.)	[121]
		kin.	[122]
		NMR	[123, 124]
3.1.4.23	Ribonuclease T_1	photoox.	[125]
		alk. (iodoacetamide)	[126]
		NMR	[127, 128]
3.1.6.1	Arylsulfatase A	kin., DEP	[129]
		azo	[130]
	Arylsulfatase B	DEP, azo	[131]
3.2.1.1	α-Amylase	kin., thermodyn.	[132]
3.2.1.2	β-Amylase	photoox.	[133]
3.2.1.4	Cellulase	kin., azo	[134]
3.2.1.26	Invertase	kin.	[135, 136]
3.4.11.1	Leucine aminopeptidase	photoox., DEP	[137]
3.4.12.2	Carboxypeptidase A	X-ray	[72, 138, 139]
3.4.12.4	Carboxypeptidase Y	alk. (Z-Phe-CK)	[140]
3.4.21.1	Chymotrypsin	kin.	[141]
		alk. (TPCK)	[142]
		photoox.	[143]
		X-ray	[144]

[a] Abbreviations: alk. = alkylation with bromoacetylarginine methyl ester (BrAc-Arg-OMe), *p*-bromophenacyl bromide (*p*-Brph.), α-halo acetates (α-Hal.), tosyllysylchloromethyl ketone (TLCK). tosylphenylalanylchloromethyl ketone (TPCK), benzyloxycarbonyl-L-phenylalanylbromomethyl ketone (Z-L-PheX) and benzyloxycarbonyl-Phe-chloromethyl ketone (Z-Phe-CK); azo. = azo coupling; DEP = diethyl dicarbonate ("diethyl pyrocarbonate"); kin. = kinetic data; P-His = *N*-phosphonohistidine; photoox. = photooxidation with methylene blue (M), pyridoxal phosphate (P) and rose bengal (R); X-ray = X-ray structure analysis; thermodyn. = thermodynamic data.

4. Enzymes with Essential Histidine Residues

Enzymes which contain essential histidine residues in their active centers are listed in Table 1; the methods employed for identification are also given. In many cases there is no doubt that additional experiments are required to verify that the histidine residues are essential for catalysis. In other cases the evidence for the direct participation of histidine residues in catalysis is irrefutable; their specialized functions are, however, still under discussion (*e.g.* pancreatic ribonuclease or papain, see below). The position of each atom in these enzymes is known but the theories as to how the catalysis proceeds at a molecular level are controversial.

In some enzymes the role of histidine has been studied especially carefully and thoroughly; chymotrypsin, pancreatic ribonuclease, papain, carboanhydrase, carboxypeptidase and

Table 1. continuation.

No. (EC)	Enzyme	Method of detection [a]	Ref.
3.4.21.4	Trypsin	kin.	[145]
		alk. (TLCK)	[146]
		alk. (bromoacetone)	[147]
3.4.21.5	Thrombin	alk. (TLCK)	[148]
3.4.21.11	Elastase	kin., X-ray	[149]
3.4.21.14	Subtilisin	kin.	[150]
		photoox.	[151]
		alk. (Z-L-PheX)	[152]
3.4.22.2	Papain	photoox.	[153–155]
		azo	[156]
		X-ray	[157]
3.4.22.3	Ficin	[c]	[158]
3.4.22.4	Bromelain	[c]	[159]
3.4.22.6	Chymopapain	photoox.	[160]
3.4.22.10	Streptococcal protease	alk. (BrAc-Arg-OMe)	[161]
3.4.24.3	Collagenase	photoox. (M)	[162]
3.4.24.4	Thermolysine	DEP	[163]
3.4.99.26	Urokinase	[d]	[164]
3.5.1.5	Urease	kin.	[165, 166]
3.5.1.14	Aminoacylase	photoox. (M)	[167]
		DEP	[168]
4.1.1.15	Glutamate decarboxylase	photoox. (P)	[169]
4.1.2.13	Fructose-bisphosphate aldolase	photoox. (P)	[170, 171]
4.1.3.8	ATP-citrate lyase	P-His	[172, 173]
4.1.99.2	Tyrosine phenol lyase	DEP	[174]
4.2.1.1	Carboanhydrase	X-ray	[71]
4.2.1.2	Fumarase	kin.	[175]
		NMR	[176]
		Affinity lab.	[177]
4.2.1.11	Enolase	photoox.	[178]
		kin.	[179]
4.2.1.24	Porphobilinogen synthase	photoox. (M), DEP	[180]
4.2.1.60	3-Hydroxyoctanoyl-[acyl carrier protein]-dehydratase	kin., alk. (bromacetate), photoox.	[181]
4.3.2.2	Adenylosuccinate lyase	photoox.	[182]
5.3.1.1	Triosephosphate isomerase	photoox.	[183]
		azo. [e]	[184]
5.3.1.8	Mannose-6-phosphate isomerase	kin.	[185]
5.3.1.9	Glucose-6-phosphate isomerase	kin.	[186]
		photoox.	[187, 188]
5.3.3.1	Δ^5-3-Ketosteroid isomerase	photoox.	[189]
		DEP	[190]
5.4.2.1	3-Phosphoglycerate mutase	[b]	[77]
6.1.1.20	Phe-tRNA synthetase	DEP, photoox. (R)	[191]
6.2.1.5	Succinate thiokinase	P-His	[75]
	Luciferase	[^{14}C]-DEP	[192, 193]
	Actin	DEP	[194]
	β-Cyclopiazonate oxidocyclase	DEP	[195]
	Phosphoenolpyruvatedependent phosphotransferase system of *Staph. aures*	NMR	[196]
	Ancrod	kin.	[197]
	Unspecific lipase	photoox. (R)	[198]
	Secotransferrin	DEP	[199]
	Lactotransferrin		
	Hemopexine	photoox. (R)	[200]
	Hemocyanine	photoox.	[201]
	Colipase	NMR	[202]
—	α-Lactalbumin	DEP	[203]
—	Ovotransferrin	DEP, photoox. (M)	[204]

[b] "Active site peptide" method.
[c] Cross linkage of the essential SH group with a histidine residue.
[d] Alkylation with chloromethyl ketone and subsequent oxidation with performic acid.
[e] Carboxymethylation.

aldolase belong to this group. The functions which can be ascribed to histidine in catalysis will now be briefly described using these examples.

In the case of the serine proteases[59] chymotrypsin, trypsin, thrombin elastase and subtilisin, it is assumed that histidine's imidazole residue takes part in a general acid-base catalysis; it facilitates the splitting off of a proton from an hydroxyl group of a serine residue or from water and thus enhances the nucleophilic reactivity of the remaining anion[60]. The interaction between imidazole and the carboxylate group of an aspartic acid residue can further increase the nucleophilicity of the serine oxygen atom *via* a "charge-relay" system and can also stabilize the tetrahedral intermediate of the catalysis (Fig. 1)[61].

General acid-base catalysis by imidazole is also assumed to occur in the cysteine proteases papain, ficin, bromelain

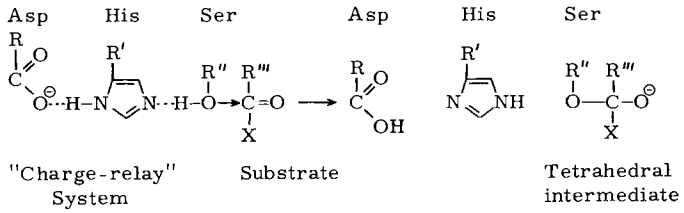


Fig. 1. Mode of action of serine proteases [59–61].

and streptococcal protease; the nature of the interaction between imidazole and the SH group is still not clear[62]. Some evidence supports a similarity with the mode of action of the serine proteases[63] (Fig. 2).

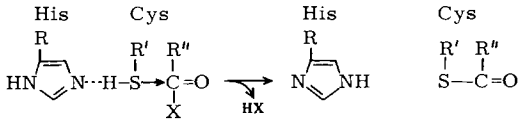


Fig. 2. Concepts of the modes of action of cysteine proteases [62, 63].

Although the exact structure of the active center of pancreatic ribonuclease is known, several reaction mechanisms are under discussion, some of which differ considerably[64]. Some authors assume that there is a general acid-base catalysis with participation of two histidine residues[65–67]; other consider that there is a hydrogen-bonded system composed of two imidazole residues which does not behave as an acid-base catalyst but only serves as part of the catalytic center to maintain the geometry of the active center and the necessary electrophilicity of a proton (Fig. 3)[68].

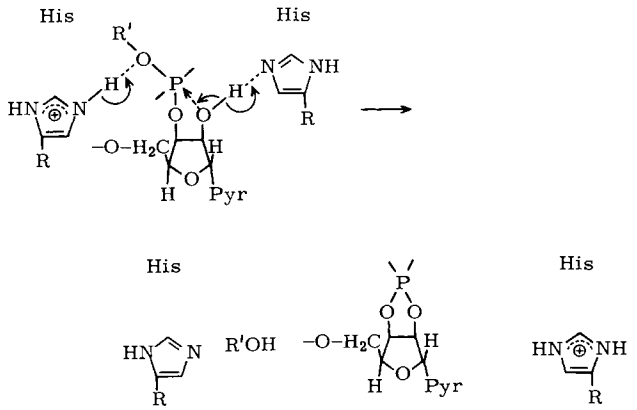


Fig. 3. Acid-base catalysis in ribonuclease [65]. Pyr = pyrimidine base.

Imidazole also acts as an agent for transferring protons to an intermediately formed carbanion in fructose-1,6-bisphosphate aldolase. This carbanion is produce from a fructose-1,6-bisphosphate by aldol cleavage and liberation of the first product, glyceraldehyde-3-phosphate (Fig. 4)[69].

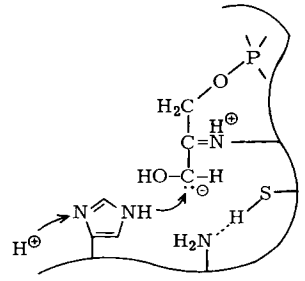


Fig. 4. Proton transfer by an imidazole residue in fructose-1,6-bisphosphate aldolase [69].

For some time the concept of concerted acid-base catalysis with involvement of imidazole residues has attracted special attention. *Jencks*[70] has, however, pointed out that concerted, general acid-base catalysis of complex reactions in aqueous solution is only possible if a marked change in the pK value occurs during the reaction and if the pK value of the catalyst lies between the initial and final pK values of the substrate. Since these criteria are often not satisfied, most reactions proceed in a stepwise and not a concerted fashion.

Carboanhydrase C from human erythrocytes is one of the enzymes which has been best investigated and in which histidine imidazole residues serve as ligands for the binding of zinc which is essential for activity. In this enzyme zinc is bound by three imidazole residues in a distorted tetrahedron whose fourth coordination site is occupied by a water molecule[71]. An imidazole residue is also involved in the binding of zinc in carboxypeptidase A[72].

As has already been mentioned in Section 2.2, *N*-phosphonohistidine has been identified as an intermediate in the enzymatic reactions of several phosphotransferases and hydrolases. Acid phosphatase[73, 74], succinate thiokinase[75], glucose-6-phosphatase[76], phosphoglycerate mutase[77], histone kinase[78] and pyruvate phosphate dikinase[79] are examples of these enzymes. Whereas in the case of acid phosphatase it must be assumed that a histidine imidazole residue participates in a nucleophilic reaction and that a phosphonohistidine is a direct intermediate in the reaction pathway from substrate to product, the significance of the phosphonohistidine demonstrated in phosphotransferases (kinases) is not totally clear. The phosphoenzyme (phosphonohistidine) seems, in at least some cases, to be a side product and not an intermediate of the enzymatic reaction[80].

Numerous enzymes containing essential histidine residues are listed in Table 1 together with the methods used to identify the histidine.

It is certain that other enzymes among the more than 1800 which have so far been classified and characterized by specific reactions will be found to contain essential histidine residues—experience shows that evolution utilizes tried and tested principles as often as possible.

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Communications are brief preliminary reports of research work in all areas of chemistry which, on account of its fundamental significance, novelty, or general applicability, should be of interest to a broad spectrum of chemists. Authors of communications are requested to state reasons of this kind justifying publication on submission of their manuscript. The same reasons should be clearly apparent from the manuscript. In cases where the editorial staff decide, after due consultation with independent referees, that these conditions are not met, manuscripts will be returned to the authors with the request to submit them for publication in a specialist journal catering for scientists working in the field concerned.

$\mathscr{S}_f$ Parameters—A Measure of the Front Strain of Alkyl Groups[**]

By *Hans-Dieter Beckhaus*[*]

The influence of structural modifications on the reactivity of molecules is often interpreted qualitatively in terms of steric effects. However, quantitative descriptions, *e.g.* as linear free-energy relationships[1], seldom prove possible. One reason is that the known steric substituent parameters E_S, E_S^c, E_S^0, $E_S^{\prime}$[1] and ν[2] are defined in terms of the rates of reference reactions. Thus they are not free from additional factors affecting reactivity. Nor do they distinguish between steric effects of different kinds, such as enthalpic and entropic effects. Whenever substituent constants reflect complex effects they suffer a loss of utility and scope[3].

A new approach to the analysis of steric affects was introduced by the use of empirical force field calculations[4]. For a number of reactions a linear relationship was established between the change in free energy of activation and the change in strain energy between the ground state and the transition state[5, 8b]. However, this procedure will not be applicable to the majority of reactions in the forseeable future owing to the incomplete parametrization of the force fields. *DeTar*[6] expediently used alkanes as models for the ground state and transition state in calculations on the acid-catalyzed esterification of carboxylic acids (cf. [9]).

In deriving new substituent constants intended as a measure of the F strain[7] of the substituents we also employed hydrocarbons as models. The F strain, *i.e.* the steric repulsion of the attacking or leaving group of a reaction, is frequently regarded (*e.g.* in the formation and hydrolysis of carboxylic esters[1], the thermolysis of highly substituted ethanes[8], the chromic acid oxidation of secondary alcohols[9a], the reduction of ketones by tetrahydridoborate[9b], and in radical reactions such as termination (cf. [8a]) and halogen transfer[10]) as the principal factor determining reactivity. The steric interaction of a substituent (R) with the core of a molecule is determined by the distance, size, and shape of the latter acting as a steric counterpart. The methyl and *tert*-butyl groups were chosen as the two alkyl groups of highest symmetry to serve as molecular core for the new steric parameters $\mathscr{S}_f(R)$. The $\mathscr{S}_f$ values [eq. (a)] were defined as the difference between the heats of formation of the *tert*-butyl derivative of R, $\Delta H_f^0[R{-}C(CH_3)_3]$, and those of the methyl derivative, $\Delta H_f^0[R{-}CH_3]$. The additive term in eq. (a) appears on normalization to $\mathscr{S}_f(CH_3)=0$.

$$\mathscr{S}_f(R)=\Delta H_f^0[R{-}C(CH_3)_3]-\Delta H_f^0[R{-}CH_3]+8.87 \quad [10^4\ \mathrm{J/mol}] \qquad (a)$$

The heats of formation were all calculated with the aid of the Engler-Schleyer force field[4b, 11]. Table 1 lists the $\mathscr{S}_f$ values of a selection of simple and cyclic alkyl groups.

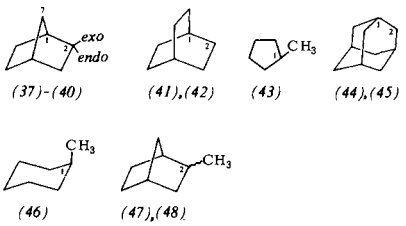


Table 1. Steric substituent constants $\mathscr{S}_f(R)$ [10^4 J/mol^{-1}] for acyclic and cyclic alkyl groups.

	R	$\mathscr{S}_f$		R	$\mathscr{S}_f$
(1)	CH_3	$\equiv 0$	(31)	*cyclo*-C_4H_7	−0.21
(2)	C_2H_5	0.86	(32)	C_8H_7 (Cubyl)	−0.04
(3)–(8)	$CH_2(CH_2)_nCH_3$ (n)	0.89(1),	(33)	*cyclo*-C_3H_5	1.33
		0.86(2),	(34)	*cyclo*-C_5H_9	1.81
		0.85(3–5),	(35)	*cyclo*-C_6H_{11}	2.29
		0.84(6)	(36)	*cyclo*-C_7H_{13}	2.94
(9)	$CH_2CH_2C(CH_3)_3$	0.85	(37)	2-*exo*-	1.83
(10)	CH_2-*cyclo*-C_6H_{11}	1.36	(38)	1-	2.57
(11)	$CH_2CH(CH_3)_2$	1.86	(39)	2-*endo*-	2.71
(12)	$CH_2C(CH_3)_3$	2.29	(40)	7-	3.11
(13)	$CH_2C(CH_3)_2C_4H_9$	3.24	(41)	2-	2.37
(14)	$CH(CH_3)_2$	2.29	(42)	1-	3.49
(15)	$CH(CH_3)C_2H_5$	2.51	(43)	1-	3.81
(16)	$CH(CH_3)CH_2C(CH_3)_3$	2.78	(44)	1-	4.08
(17)	$CH(CH_3)C_6H_{13}$	2.87	(45)	2-	4.45
(18)	$CH(C_2H_5)_2$	3.29	(46)	1-	4.92
(19)	$CH(CH_3)C(CH_3)_3$	4.93	(47)	2-*exo*-	4.98
(20)	$CH[CH(CH_3)_2]_2$	5.61	(48)	2-*endo*	6.20
(21)	$CH(C_2H_5)C(CH_3)_3$	7.26			
(22)	$CH(C(CH_3)_3)_2$	10.68			
(23)	CH(1-Adamantyl)$_2$	12.65			
(24)	$C(CH_3)_3$	3.82			
(25)	$C(CH_3)_2C_2H_5$	4.36			
(26)	$C(CH_3)_2CH_2C(CH_3)_3$	4.40			
(27)	$C(CH_3)_2C_8H_{17}$	4.85			
(28)	$C(CH_3)(C_2H_5)_2$	5.26			
(29)	$C(C_2H_5)_3$	6.28			
(30)	$C(CH_3)_2C(CH_3)_3$	7.51			

The $\mathscr{S}_f$ constants reflect only the steric repulsion of the groups R by a symmetrical counterpart and therefore contain no additional conformational effects such as "gear"[12a] or "cogwheel" effects[12b]. They are therefore ideally suited for the analysis of reactions in which no "gear" effects are operative alongside the F strain. Such a situation is expected in the exothermic reactions of radicals such as termination and halogen transfer[10b].

Moreover, $\mathscr{S}_f$ values should be useful in detecting "gear"-type interactions between substituents and the reaction center.

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This will be demonstrated for the acid-catalyzed esterification of carboxylic acids.

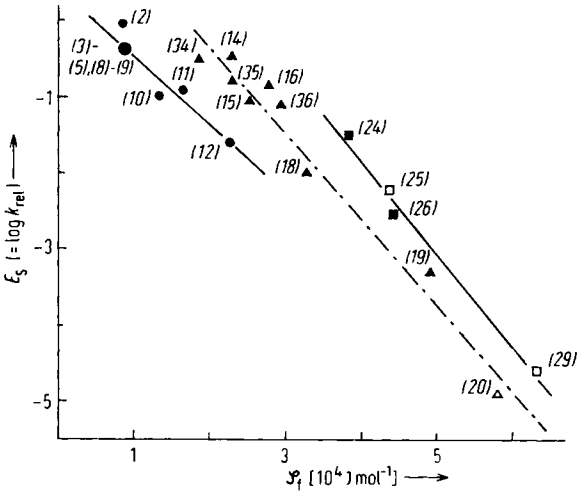


Fig. 1. Correlation of the E_S values (= $\log k_{rel}$) for acid-catalyzed esterification of carboxylic acids (R—COOH) with $\mathcal{S}_f$ values; values corresponding to the open symbols were taken from *P. J. Sniegoski*, J. Org. Chem. *41*, 2058 (1976), and the other from [1]. Correlation coefficients: R = *prim*-alkyl (●), $r = -0.962$ (9 values); R = *sec*-alkyl (▲), $r = -0.972$ (9 values); R = *tert*-alkyl (■), $r = -0.994$ (4 values). The differences in the intercepts are highly significant according to the Student's T test (confidence limits 99.9%).

This reaction is subject to steric hindrance by an increase in steric strain on transformation of the carbonyl C atom of the carboxylic acid into a four-coordinate C atom in the transition state[1, 6]. In the ground state the alkyl groups R can avoid the repulsion exerted by the flat carboxyl group to various degrees, depending upon the number of substituents present on the α-C atom of R, by rotation about the R—COOH bond. The α-substituent in primary R can always find a "conformational gap", the two α-substituents in secondary R can avoid interaction less easily, while the tertiary groups R experience the full effect of repulsion. These possible ways of evasion are limited in the transition state and should therefore appear as differences in reactivity. Correlation of the reaction rates ($\log k_{rel} = E_S$) with the $\mathcal{S}_f$ parameters gives linear plots for primary, secondary, and tertiary groups R with similar slopes but significantly different intercepts (Fig. 1). This is to be regarded as an indication that the E_S parameters include an additional effect depending upon the number of H atoms attached to the α-C atom of R. Most likely this effect is due mainly to the special conformational features of the carboxylic acids.

As may be seen from this and another example[10b], $\mathcal{S}_f$ values prove to be a useful tool for the analysis of F strain effects on reactivity. They are easily calculated even for very bulky groups, *e.g. (24)* and *(25)*, and numerous unsaturated[11b] hydrocarbon groups.

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[11] a) The energy unit 10^4 J/mol was chosen in order to provide convenient numerical values for the $\mathcal{S}_f$ parameters. b) The analogous differences ΔH_f^0(R—*t*Bu) − ΔH_f^0(R—Me) calculated with a force field according to *Allinger* (1971) [4c] could be correlated linearly with the $\mathcal{S}_f$ values (slope $a = 1.06$). Hence the calculation of $\mathcal{S}_f$ values for alkenyl groups and groups containing phenyl rings [4d] is possible in principle.

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Front Strain of π and σ Radicals[**]

By *Bernd Giese* and *Hans-Dieter Beckhaus*[*]

Radicals are classified as planar π radicals (1) and nonplanar σ radicals *(2)*.



(1) *(2)*

It was deduced from the temperature dependence of the ^{13}C and ^1H coupling constants of ESR spectra[1] that the pyramidal conformation becomes energetically more favorable with increasing alkylation of the radical carbon atom[2]. While the methyl radical is planar (π radical), the *tert*-butyl radical should possess almost tetrahedral geometry (σ radical)[1, 2]. More recent studies have shown that the bending of the *tert*-butyl radical is caused by solvents at low temperature[3]. In the absence of this matrix effect the *tert*-butyl radical should have planar geometry, like the methyl radical[3].

Evidence for a common structure of alkyl radicals above 273 K in solvents of low polarity such as CCl_4 is also provided by our observation[4] that the reactions of methyl and of

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prim-, *sec*-, and *tert*-alkyl radicals in the competition system $BrCCl_3/CCl_4$

$$RCl \xleftarrow[\Delta H^{\ddagger}_{Cl}]{CCl_4} \underset{(3)}{R\bullet} \xrightarrow[\Delta H^{\ddagger}_{Br}]{BrCCl_3} RBr \qquad (a)$$

can be described by a common isoselective relationship[4] which differs significantly from the isoselective relationship of σ radicals.

In order to gain a further insight into the preferred conformation of alkyl radials we have developed a method based on the various degrees of steric shielding of the radical carbon atoms. Thus, owing to their planar geometry π radicals *(1)* should have a greater F strain than similarly substituted σ radicals *(2)* because the latters' substituents will be bent away from the frontside. The F strain of the groups R can be calculated from the differences between the heats of formation of the hydrocarbons *(4)* and *(5)*[5]. A suitable radical reaction is halogen capture according to eq. (a) which is controlled by steric parameters of the radicals *(3)*[6].

$R-C(CH_3)_3$ *(4)* $\qquad$ $R-CH_3$ *(5)*

Plotting the experimentally determined activation energies $\Delta H^{\ddagger}_{Cl} - \Delta H^{\ddagger}_{Br}$ of the competing radical reaction (a) *versus* the values of the F strain $\mathcal{S}_f$ calculated from *(4)* and *(5)* gives two straight lines (Fig. 1).

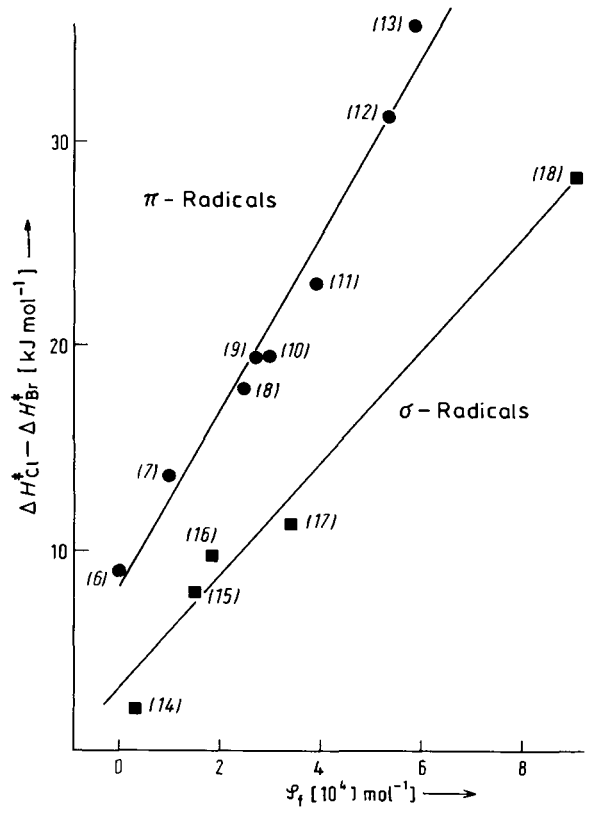


Fig. 1. Variation of the differences in activation energies $\Delta H^{\ddagger}_{Cl} - \Delta H^{\ddagger}_{Br}$ of halogen abstraction (a) with the values of F strain $\mathcal{S}_f$ calculated from the differences in heats of formation of *(4)* and *(5)*. *(6)*: CH_3, *(7)*: 1-$C_6H^{\bullet}_{13}$, *(8)*: *c*-$C_6H^{\bullet}_{11}$, *(9)*: 2-bicyclo[2.2.2]octyl, *(10)*: 2-$C_8H^{\bullet}_{17}$, *(11)*: $C_4H_9C(CH_3)_2\dot{C}H_2$, *(12)*: $C_8H_{17}\dot{C}(CH_3)_2$, *(13)*: $CH_3\dot{C}(C_2H_5)_2$, *(14)*: $CH_2{=}\dot{C}H$, *(15)*: *c*-$C_3H^{\bullet}_5$, *(16)*: $C_6H^{\bullet}_5$, *(17)*: 7-norbornyl, *(18)*: 2-*t*-$C_4H_9C_6H^{\bullet}_4$.

The lower, less steep line represents the σ radicals whose carbon atoms do not have a planar conformation either in the radical *(3)* or in the hydrocarbons *(4)* and *(5)*. The steeper slope of the upper line shows that the corresponding radicals have a larger F strain than is calculated for the nonplanar hydrocarbons *(4)* and *(5)*. In the transition state of halogen abstraction (a) the radicals *(6)*—*(13)* therefore exert a comparatively greater repulsion on the halogen transfer agent $XCCl_3$ (X = Cl, Br) than the σ radicals *(14)*—*(18)*. These differing steric effects indicate that there is only slight pyramidalization, if any, in the radicals *(6)*—*(13)*. Not only the methyl radical *(6)* but also the *prim*-, *sec*-, and *tert*-alkyl radicals *(7)*—*(13)* are therefore largely planar above 273 K. A transition from planar to tetrahedral conformation with increasing number of alkyl substituents[2] cannot be reconciled with our experimental results.

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Temperature Dependence of Carbene Selectivities: A New Example of the Isoselective Relationship[**]

By *Bernd Giese* and *Jürgen Meister*[*]

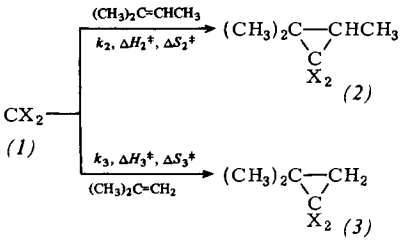
Hardly any absolute rate constants have been published so far for carbene reactions[1]. Selectivity values (relative reactivities) therefore usually have to be employed in interpreting such reactions[2]. However, this can lead to serious errors if temperature effects are disregarded. For example, several series of reactions are known in which the selectivities of molecules become equal in a narrow temperature range, the

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isoselective temperature T_{is}[3]. Above and below T_{is} the order of selectivities is reversed.

It was recently suspected that the isoselective temperature can lie within the range of experimental determination for carbenes too[3,4]. We have now studied the cycloadditions of difluorocarbene *(1a)*, dichlorocarbene *(1b)*, and dibromocarbene *(1c)* in the 2-methyl-2-butene/2-methylpropene competition system between 233 and 433 K.



(a), X = F; *(b)*, X = Cl; *(c)*, X = Br

The carbenes *(1a—c)* were generated in the temperature range 353 to 433 K from the corresponding trihalomethyl(phenyl)mercury derivatives by the method of *Seyferth*[5a]. Reaction of CHX_3 (X = Cl, Br) with bases such as $(CH_3)_3COK$ was found to be a better method for generating CX_2 (X = Cl, Br) below 353 K[5b]. The selectivity values of the difluorocarbenes generated from difluorodiazirine at 309 and 364 K were taken from the literature[6]. We employed an at least 10-fold excess of the 2-methyl-2-butene/2-methylpropene competition pair in formation and reaction of the carbenes in order that the selectivities ($\log k_2 - \log k_3$) could be determined over large temperature ranges from the ratio of cyclopropanes *(2)*/*(3)* (gas chromatography) according to eq. (A) (Fig. 1).

$$\frac{k_2}{k_3} = \frac{[(2)][(CH_3)_2C{=}CH_2]}{[(3)][(CH_3)_2C{=}CHCH_3]} \qquad (A)$$

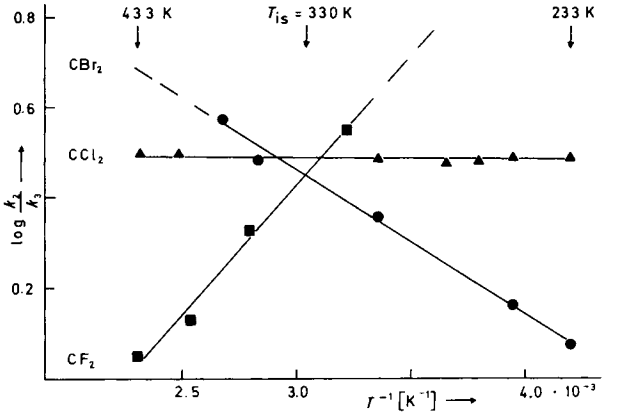


Fig. 1. Temperature dependence of the selectivities ($\log k_2/k_3$) of the carbenes CX_2 (X = F, Cl, Br) in 2-methyl-2-butene/2-methylpropene as competition system [7].

Whereas *(1a)* is the most selective of the carbenes studied below 330 K (order of selectivity: $CF_2 > CCl_2 > CBr_2$), the selectivities assume the same values in the temperature range 330 ± 15 K ($CF_2 = CCl_2 = CBr_2$). Above this temperature *(1c)* is the most selective species ($CF_2 < CCl_2 < CBr_2$). Conclusions concerning differences in reactivities or stabilities of the individual carbenes from experimentally available selectivities are possible only if this influence of temperature is observed. The temperature dependence of the selectivity sequence is due to changes in activation enthalpies, and entropies which are therefore more suitable experimental data for the interpretation of reaction mechanisms[3].

Table 1. Differences in enthalpies of activation $\Delta H_3^{\ddagger} - \Delta H_2^{\ddagger}$ [kJ mol^{-1}] and entropies of activation $\Delta S_3^{\ddagger} - \Delta S_2^{\ddagger}$ [J mol^{-1} K^{-1}] of the carbenes *(1a—c)* in the competition system 2-methyl-2-butene/2-methylpropene.

Carbene	$\Delta H_3^{\ddagger} - \Delta H_2^{\ddagger}$ [a]	$\Delta S_3^{\ddagger} - \Delta S_2^{\ddagger}$ [b]
CF_2	11	26
CCl_2	0.0	− 9.5
CBr_2	−6.1	−27

[a] Mean error ±7%.
[b] Mean error ±5 J mol^{-1} K^{-1}.

Thus the data compiled in Table 1 show that the activation enthalpy $\Delta H_2^{\ddagger}$ for reaction with the sterically more shielded 2-methyl-2-butene becomes less favorable relative to $\Delta H_3^{\ddagger}$ (reaction with 2-methylpropene) with increasing bulkiness of the carbenes ($CF_2 < CCl_2 < CBr_2$). The electrophilic character of CCl_2 and CBr_2, *i.e.* their greater reactivity towards the more nucleophilic 2-methyl-2-butene, is due to entropic effects[9]. In the case of CBr_2, the faster reaction even has the greater activation enthalpy (cf. Table 1).

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CAS Registry numbers:
(1a), 2154-59-8; *(1b)*, 1605-72-7; *(1c)*, 4371-77-1

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[6] *R. A. Mitch*, Int. J. Chem. Kinet. *1*, 439 (1969).
[7] The selectivities of CF_2 at 309 and 364 were taken from the literature [6]. Earlier values for the selectivity of CCl_2 (at 263 [8], 273, and 298 K [2]) were confirmed.
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[9] Reactions with substituted styrenes indicate that the polar effects of the carbenes have a considerable influence on the entropies of activation.

Preparation and Crystal Structure of $Pd_2Mo_2(\eta^5\text{-}C_5H_5)_2(\mu_3\text{-}CO)_2(\mu_2\text{-}CO)_4(PEt_3)_2$. A Planar, Triangulated, Palladium-Molybdenum-Carbonyl Cluster[1]

By *Robert Bender, Pierre Braunstein, Yves Dusausoy*, and *Jean Protas*[*]

trans-$Pdpy_2Cl_2$ reacts with η^5-$C_5H_5Mo(CO)_3^-$, $Co(CO)_4^-$, and $Mn(CO)_5^-$ to afford the linear metal-metal bonded complexes Mo—$Pd(py)_2$—Mo[2], Co—$Pd(py)_2$—Co, and Mn—$Pd(py)_2$—Mn[3].

We have now found that reaction of *trans*-$Pd(PEt_3)_2Cl_2$ with η^5-$C_5H_5Mo(CO)_3^-$ follows a different route owing to the lability of the phosphane moiety. Thus we obtained the heterotetra-

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metallic $Pd_2Mo_2(\eta^5\text{-}C_5H_5)_2(\mu_3\text{-}CO)_2(\mu_2\text{-}CO)_4(PEt_3)_2$ cluster *(1)* instead of a linear trimetallic complex. Complexes $\eta^5\text{-}C_5H_5(OC)_3Mo\text{—}Mo(CO)_2(PEt_3)\eta^5\text{-}C_5H_5$ *(2)* and *(1)* are the only products isolated[4]. The structure of *(1)* was elucidated by X-ray crystallography (Fig. 1)[5].

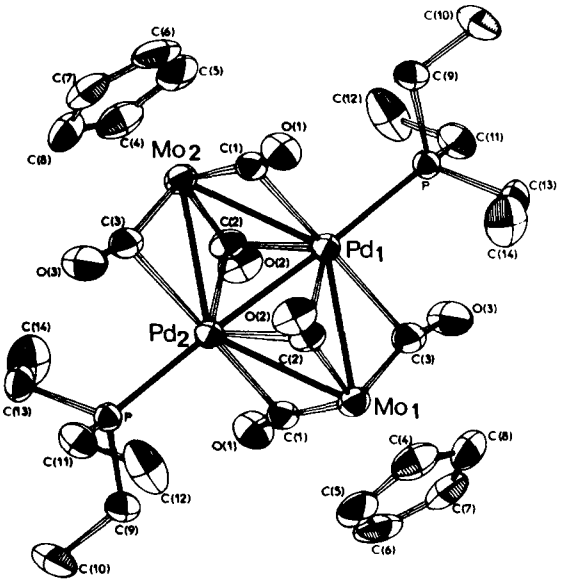


Fig. 1. Structure of the molecule *(1)*; metal-metal bond lengths in [pm]: Pd(1)—Mo(1), 282.7(1); Pd(1)—Mo(2), 286.5(1); Pd(1)—Pd(2), 258.2(1).

The four metal atoms in *(1)* form a planar, triangulated frame, with a center of symmetry in the middle of the Pd—Pd bond. There is one triply bridging μ_3-CO group on each Pd_2Mo triangle [ν(CO) (cm^{-1}) in KBr: 1772 cm^{-1} (vs)] and one bridging μ_2-CO group on each PdMo bond [ν(CO) (cm^{-1}) in KBr: 1842 (vs) and 1801 cm^{-1} (m)]. Each of the two $\eta^5\text{-}C_5H_5$ rings is bonded to a Mo atom and forms an angle of 74.7° with the plane of the metal atoms, whereas the PEt_3 ligands are bonded to the Pd atoms and are collinear with the Pd—Pd bond.

In the 68-electron cluster *(1)*, the presence of two 18 electron Pd and two 16 electron Mo atoms accounts for the five metal-metal bonds. This cluster and its structure appear very significant for the following reasons:

1) each Pd atom has the unusual coordination number eight;

2) it is the first example of an *hetero*polymetallic palladium cluster;

3) it permits the third determination of the metal-metal bond distance between palladium and another transition metal (Pd—Fe[6a], Pd—Co[6b]);

4) the only other reported example of a planar, triangulated cluster is the *homo*tetrametallic $[Re_4(CO)_{16}]^{2-}$ complex[7].

Experimental

All reactions and operations were carried out under nitrogen. Solvents were dried and distilled under nitrogen before use. A tetrahydrofuran solution (60 ml) of $Na[Mo(\eta\text{-}C_5H_5)(CO)_3]$, prepared from $[\eta\text{-}C_5H_5Mo(CO)_3]_2$[8] (2.15 g, 5 mmol), was filtered and added to a suspension of *trans*-$Pd(PEt_3)_2Cl_2$ (2.06 g, 5 mmol) in THF (50 ml) at room temperature. This mixture was stirred for 7.5 h. The residue obtained after filtration and evaporation under reduced pressure was chromatographed on a silica gel column (Kieselgel 60, Merck). Elution with toluene/pentane (1 : 10) gave a pale yellow compound which was not further investigated. Further elution with toluene/pentane (1 : 2) gives a red-mauve solution of *(2)*, which can be recrystallized from toluene/pentane. Yield 0.03 g (0.5 %). With toluene, a dark violet solution was collected which afforded *(1)* as dark-violet crystals from toluene/pentane or CH_2Cl_2/pentane, m.p. 193—196 °C (decomp.); yield 1.75 g (75 % based on Pd, 40 % based on Mo).

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CAS Registry numbers:
(1), 67254-46-0; $Na[Mo(\eta^5\text{-}C_5H_5)(CO)_3]$, 12107-35-6; *trans*-$Pd(PEt_3)_2Cl_2$, 15642-19-0

[1] Organometallic Complexes with Metal-Metal Bonds, Part 10. The Laboratoire de Chimie de Coordination acknowledges financial support from the Centre National de la Recherche Scientifique (ATP 2645).—Part 9: *J. P. Barbier, P. Braunstein, J. Fischer, L. Ricard*, in press.

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[4] The new compounds were isolated and characterized by elemental analysis (C, H, P), IR, ^{1}H- and ^{31}P-NMR spectroscopy.

[5] Monoclinic crystals, space group $P2_1/c$, $Z=2$, $a=10.924(2)$, $b=9.474(2)$, $c=17.596(5)$ Å, $\beta=114.89(2)°$, $V=1775.7$ Å^3. 4134 reflections were recorded in the range $1° < \theta < 27°$ using graphite monochromated $Mo_{K\alpha}$ radiation. 3179 of these ($I > \sigma I$) were used in structure solution and refinement; $R=0.032$.

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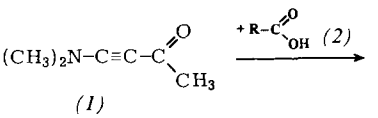
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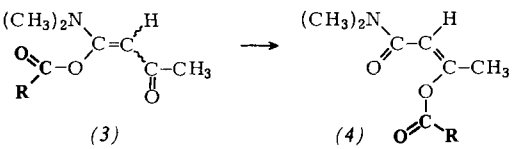
4-Dimethylamino-3-butyn-2-one as Activating Agent for Peptide Synthesis[**]

By *Hans-Joachim Gais*[*]

The chemoselective activation of carboxyl groups in polyfunctional molecules is very easily accomplished with 4-dimethylamino-3-butyn-2-one *(1)*[1]. The resulting activated enol esters *(4)* have proved to be excellent acyl transfer agents, *e.g.* in the synthesis of thiol and selenol esters[1].



(1)



(3) *(4)*

It appeared tempting, therefore, to test the utility of the acetylene derivative *(1)* as activating agent for peptide synthesis. We found that *(1)* readily reacts with *N*-acylamino acids *(2a—i)* or *N*-acylpeptides *(2j—m)* in anhydrous aprotic solvents at −60 to 0 °C to give the *N*-acylamino acid- *(4a—i)* or *N*-acylpeptide (*Z*)-1-methyl-2-dimethylcarbamoyl vinyl esters *(4j—m)* in almost quantitative yields (Table 1)[2]. In general, these esters are readily crystallizable, hydrolysis-stable, and, up to *(4e)*, air-stable compounds. The non-isolable primary adducts *(3)* cannot be detected NMR spectroscopically, even at −60 °C[1].

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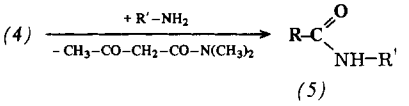
[**] Part of a lecture delivered at the Chemiedozententagung in Berlin, April 5, 1978.

Table 1. *N*-Acylamino acid- *(4a—i)* and *N*-acylpeptide (*Z*)-1-methyl-2-dimethylcarbamoylvinyl esters *(4j—m)*.

N-Acylamino acid or *N*-acylamino peptide		Enol ester	Yield [%] [a]
(2a)	Boc-L-Tyr	*(4a)*	97
(2b)	Boc-L-Ser	*(4b)*	96
(2c)	Z-L-Ser	*(4c)*	97
(2d)	Z-L-Hyp	*(4d)*	98
(2e)	Ac-L-Cys	*(4e)*	92 [b] [c]
(2f)	Z-L-Gln	*(4f)*	94
(2g)	Boc-L-Asn	*(4g)*	91
(2h)	Z-L-Phe	*(4h)*	98
(2i)	Bz-L-Leu	*(4i)*	99
(2j)	Z-Gly-L-Phe	*(4j)*	95
(2k)	Boc-Gly-L-Pro	*(4k)*	93
(2l)	Z-Gly-L-Met	*(4l)*	96
(2m)	Z-L-Leu-L-Val	*(4m)*	96

[a] The yields refer to isolated pure compounds.
[b] Rearranges at room temperature with loss of *N*,*N*-dimethylacetoacetamide.
[c] Determined NMR spectroscopically.

The chemoselective activation of the carboxyl group in Boc-tyrosine *(2a)*, Boc-serine *(2b)*, Z-hydroxyproline *(2d)*, Ac-cysteine *(2e)*, Z-glutamine *(2f)* and Boc-asparagine *(2g)* proceeds smoothly, and the unprotected side-chain functions are not attacked even by an excess of *(1)*. With less than equimolar amounts of *(1)*, no carboxylic anhydride is formed. The activated esters *(4)* react both with amino acid esters and with amino acid ester hydrochloride/triethylamine within a few hours at −10 to 0°C to give the *N*-acylpeptide esters *(5)*[3] in very high yields (Table 2)[2].



(5)

Table 2. *N*-Acyldi-*(5a—i)* and *N*-acyltripeptide esters *(5j—n)*.

Enol ester		*N*-Acyl peptide ester	Yield [%] [b]
(4a)	*(5a)*	Boc-L-Tyr|Gly-OEt	97
(4b)	*(5b)*	Boc-L-Ser|Gly-OEt	97
(4d)	*(5c)*	Z-L-Hyp|Gly-OEt	94
(4d)	*(5d)*	Z-L-Hyp|L-Leu-OMe	96
(4e)	*(5e)*	Ac-L-Cys|Gly-OEt	87
(4e)	*(5f)*	Ac-L-Cys|L-Leu-OMe	93
(4f)	*(5g)*	Z-L-Gln|L-Leu-OMe	93
(4g)	*(5h)*	Boc-L-Asn|L-Leu-OMe	91
(4i)	*(5i)*	Bz-L-Leu|Gly-OEt	95
(4j)	*(5j)*	Z-Gly-L-Phe|Gly-OEt	97
(4k)	*(5k)*	Boc-Gly-L-Pro|L-Leu-OMe	96
(4l)	*(5l)*	Z-Gly-L-Met|Gly-OEt	97
(4m)	*(5m)*	Z-L-Leu-L-Val|Gly-OEt	95
(4m)	*(5n)*	Z-L-Leu-Val|L-Leu-OMe	98

[a] The amide bond being formed is indicated by a vertical line.
[b] The yields refer to isolated pure compounds.

In most cases the crude products are crystalline and already analytically pure. The facile and clean synthesis of peptides *(5)* from the amino acids *(2)* with unprotected side-chain functions deserves special mention. The *N*,*N*-dimethylacetoacetamide formed along with *(5)* is readily soluble in water, carbon tetrachloride and ether and thus can be easily separated from hydrophobic and hydrophilic products. The synthesis of *(5)* from *(2)* can also be carried out as a one-pot reaction.

Of crucial importance is the racemization-free formation of the amide bond. On IR spectroscopic investigation of the synthesis of the enol ester from hippuric acid and *(1)* no azlactone formation was observed (Woodward test[4]), which is generally held responsible for the racemization[5]. In accord with this finding the very sensitive Young test[6], modified according to Anderson[7], shows that no racemization takes place in the synthesis of *(5i)* from *(4i)* and glycine ethyl ester-hydrochloride/triethylamine. According to the Anderson test[8] *(5j)* is also formed without racemization.

General Procedure

N-Benzyloxycarbonyl-L-serine (*Z*)-1-methyl-2-dimethylcarbamoylvinyl ester *(4c)*: A solution of *(2c)* (2.39 g, 10.0 mmol) in anhydrous THF (50 ml) is added dropwise with stirring at −30°C to a solution of *(1)* (1.12 g, 10.1 mmol) in anhydrous THF (30 ml) in the absence of moisture. After 30 minutes' stirring at −30°C the reaction solution is warmed to room temperature and the solvent removed by evaporation *in vacuo*. Recrystallization of the crystalline residue from ethyl acetate/*n*-hexane affords 3.39 g (97%) *(4c)*, colorless crystals, m.p. 109—110°C, $[\alpha]_D^{23} = -99.7°$ (2, $CHCl_3$), ^{1}H-NMR (60 MHz, [D_6]-DMSO, δ rel. TMS int). 1.94 (d, $J = 0.7$ Hz, 3H), 2.81 (s, 3H), 2.97 (s, 3H), 3.66 (m, 2H), 4.26 (m, 1H), 4.95 (t, $J = 7$ Hz, 1H), 5.10 (s, 2H), 6.00 (q, $J = 0.7$ Hz, 1H), 7.40 (s, 5H), 7.48 (m, 1H).

N-Benzoyl-L-leucyl-glycine ethyl ester *(5i)*: A solution of *(2i)* [m.p. 103.5—105°C, $[\alpha]_D^{23} = -7.0°$ (2.6, C_2H_5OH)] (2.35 g, 10.0 mmol) in anhydrous THF (50 ml) is added dropwise with stirring at −30°C to a solution of *(1)* (1.12 g, 10.1 mmol) in anhydrous THF (30 ml) in the absence of moisture. After 30 min at −30°C the reaction solution is warmed to 0°C, treated with 1.53 g (11.0 mmol) glycine ethyl ester-hydrochloride and 1.53 ml (11.0 mmol) anhydrous triethylamine, and stirring continued for 12 h at room temperature. After removal of solvent *in vacuo*, the residue is taken up in 100 ml ethyl acetate and the resulting solution washed with water, saturated $NaHCO_3$ solution, 1 N hydrochloric acid and brine, and finally dried over $MgSO_4$. Removal of solvent *in vacuo* affords 3.04 g (95%) *(5i)*, colorless crystals, m.p. 155.5—156.5°C, $[\alpha]_D^{23} = -33.7°$ (3, C_2H_5OH) (−33.5°[7]).

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Ethylenebis(diphenylphosphane)dihydrogenselenidonickel(II)

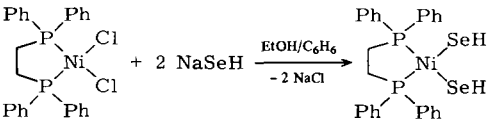
By *Max Schmidt* and *Gerhard G. Hoffmann*[*]

Paramagnetic nickel(I) complexes containing SH-, SR-, or SeH-ligands have recently been described[1]. This has prompted us to report on the first results of studies aimed,

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inter alia, at the synthesis and investigation of previously unknown "acidic transition metal selenides" of the type $L_xM(SeH)_y$.

Our attempts to convert dichloroethylenebis(diphenylphosphane)nickel(II) *(1)* into (diphos)Ni$(SH)_2$ with hydrogen sulfide have, in contrast to reactions of comparable palladium(II) and platinum(II) compounds[2], so far failed (mainly NiS formation). Surprisingly, however, we have been able to synthesize the homologous complex (diphos)Ni$(SeH)_2$ *(2)* by reaction of *(1)* with sodium hydrogen selenide in ethanol/benzene according to



(1) *(2)*

The new compound *(2)* is the first hydrogen chalcogenide of nickel(II). The reddish-brown, tetracoordinated d^8-complex is insoluble in unchlorinated hydrocarbons, alcohols, and water. In the solid state it is astonishingly air-stable, despite the two vicinal HSe groups; decomposition, with, *inter alia*, evolution of H_2Se, is only observed above *ca.* 100 °C (the DTA diagram shows a second maximum at 146 °C).

Solutions of *(2)* in CH_2Cl_2 or $CHCl_3$, on the other hand, decompose slowly in the presence of air (formation of a black precipitate). The clearly identifiable ^{1}H-NMR spectrum ($CDCl_3$, TMS int.) shows a singlet for the SeH protons at $\delta = 1.7$. In the IR spectrum (Nujol) the SeH stretching vibration appears at 2259 cm^{-1}; the bands at 249 and 209 cm^{-1} are assigned to the Ni—Se stretching vibrations.

Procedure

To a solution of 5.00 mmol sodium hydrogen selenide [prepared from 0.39 g (5.00 mmol) selenium and 0.2 g (5.30 mmol) sodium tetrahydridoborate] in 25 ml ethanol and 10 mol benzene is added 1.30 g (2.50 mmol) (diphos)$NiCl_2$ *(1)* under an atmosphere of N_2; the resulting suspension slowly turns rusty-brown in color. After stirring for 0.5 h it is filtered, washed with water, ethanol and *n*-hexane, and dried over P_4O_{10}. Yield 81.2 %. The elemental analysis (C, H, Ni, Se) of the product corresponds to the composition of *(2)*.

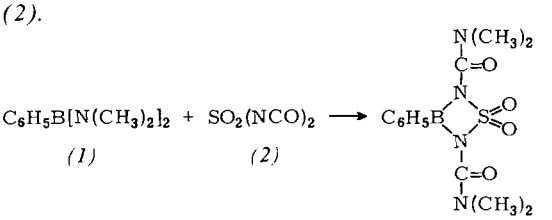
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[1] *C. Mealli, S. Midollini, L. Sacconi*, Inorg. Chem. *17*, 632 (1978).
[2] *M. Schmidt, G. G. Hoffmann*, Z. Naturforsch., in press.

2,4-Bis(dimethylcarbamoyl)-1,1-dioxo-3-phenyl-1λ^6,2,4,3-thiadiazaboretidine: a BN_2S Ring by "Insertion" of Sulfonyl Diisocyanate[**]

By *Herbert W. Roesky* and *Sushil K. Mehrotra*[*]

Four-membered boron-nitrogen heterocycles have been well documented[1, 2]; however, no compounds having sulfur in the ring have so far been described[3]. In connection with our studies on sulfur-nitrogen compounds we were interested in the combination of electron-rich and electron-deficient elements, in order to obtain further information about the bonding in such systems. We have now been able to synthesize the thiadiazaboretidine *(3)* in quantitative yield by reaction of bis(dimethylamino)phenylborane *(1)* with sulfonyl diisocyanate *(2)*.



(3)

The amorphous, white solid product *(3)* is sensitive to hydrolysis and is soluble in benzene. The mass spectrum (70 eV) shows the molecular ion of *(3)* at $m/e = 324$ (31 % rel. int.) and $(CH_3)_2NCO^+$ as base peak at $m/e = 72$ (100 %). The ^{1}H-NMR spectrum shows the expected singlet at $\delta = 3.52$ for the methyl protons and a multiplet at $\delta = 7.84$ (TMS ext.) for the phenyl protons. The absorptions observed at 1620 and 1597 cm^{-1} in the IR spectrum are assigned to the C=O stretching vibrations. Both the IR and mass spectra as well as the high solubility of *(3)* in weakly polar solvents are inconsistent with the alternative structure of a dipolar addition product.

Procedure

A solution of *(2)* (2.81 g, 18 mmol) in CH_2Cl_2 (10 ml) is added to a solution of *(1)* (3.3 g, 18 mmol) at room temperature. Reaction is exothermic, and a colorless solution is obtained. After one hour's stirring the solvent is removed *in vacuo* without application of heat. The white residue is taken up in a little benzene and the solution filtered and finally concentrated by evaporation. *(3)* precipitates; yield 5.9 g (97 %), m.p. 197—200 °C. The composition of the compound is confirmed by elemental analysis (C, H, B, N and S).

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CAS Registry numbers:
(1), 1201-45-2; *(2)*, 4223-09-0; *(3)*, 67194-36-9

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

An Unusually Versatile Solid-State Structure: Polyiodides of Type $Tl_6I_6M^{n+}_{2/n}(I_4)^{2-}$ (M = Ag, Au, Tl, Pb, Bi, Ln, Zr, Hf, Th)

By *Albrecht Rabenau* and *Wolfgang Stoeger*[*]

In the polyiodide $Tl_6I_6Pb^{2+}(I_4)^{2-}$ (Tl_6PbI_{10})[1] three channels are formed per unit cell of the skeletal structure parallel to the hexagonal *c*-axis (space group $P\bar{6}2c$). One of the channels consists of a column of face-sharing I_6 octahedra

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in which the Pb^{2+} ions are arranged linearly. In the two other channels the linear array of iodine atoms of the polyiodide group are coordinated by thallium in a distorted octahedral arrangement (cf. Fig. 1).

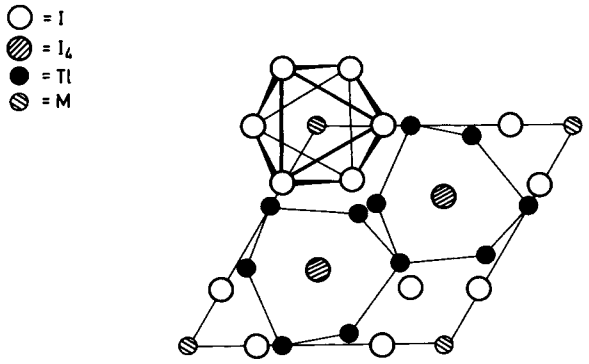


Fig. 1. Projection along [001]. The boundary of the unit cell and the atoms of the channel wall are joined by lines. I_6 octahedron outlined perspectively.

The similarity between this structure and that of the superposed structure of Tl_3I_4[2], in which thallium replaces lead, would immediately suggest that variation in the occupation of the octahedral columns is possible. We have in fact confirmed this concept in numerous examples, and observed that there is unusually large tolerance regarding the size, charge, and electronic configuration of the species M. According to single crystal structure analyses already carried out on some of the compounds the channels are extremely flexible regarding the accommodation of cations. While bismuth occupies the octahedral centers, in the case of lead[1b] and silver[3a] the atoms are displaced somewhat from the octahedral centers, leading in the latter case to pair formation. On the other hand, in the case of gold[3b] 5/6 of the atoms lie in triply-coordinated positions in the faces shared by adjacent octahedra.

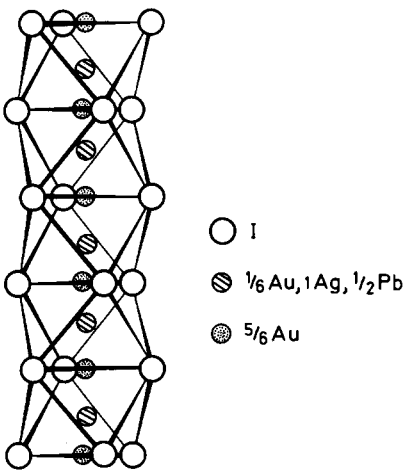


Fig. 2. Distribution of the metals M within the I_6 octahedral column with accommodation possibilities (idealized).

The polyiodide atoms accommodate to the type and occupation of the cationic sites. Whereas equidistant I_4^{2-} groups are present in the lead compound, in the silver compound the bond lengths are clearly different, corresponding to the situation in $Cu(NH_3)_4I_4$[2,4]. In the gold compound the combination I_3^-, I predominates over I_4^{2-}.

The results of further structural investigations should prove interesting, especially in the case of the lanthanoid (Ln) compounds and Zr^{4+} and Th^{4+}. A compilation of results available thus far is given in Table 1. The extraordinary versatility regarding the physical properties of this "model structure", in which a one-dimensional arrangement of very different ions is possible, is immediately recognizable. The preparative scope of such a structure can obviously be extended even further through solid solution formation. Obviously, the combination $M^{\geq 3+}$, Tl^+ contributes to the stability of this structure. Its belonging to a symmetry class without a symmetry center ($\bar{6}2m$) is also of interest in this connection.

Table 1. Polyiodides of type $Tl_6I_6M^{n+}_{2/n}(I_4)^{2-}$

1.1. Single crystal data.

Cation M^{n+}	Radius [Å]	Lattice constants [a] a [Å]	c [Å]	M.p. (dec.) [°C]
Ag^+	1.26	10.48	6.71	301
Au^+	1.37	10.57	6.72	275
Pb^{2+}	1.20	10.56	6.76	346
Bi^{3+}	0.96	10.37	6.84	323

1.2. Polycrystalline samples [7]

Cation M^{n+}	Radius [Å]	M.p. (dec.) [°C]	Cation M^{n+}	Radius [Å]	M.p. (dec.) [°C]
La^{3+}	1.15	282	Eu^{2+}	1.12	297
Pr^{3+}	1.00	297	Th^{4+}	0.95	263
Nd^{3+}	0.99	307	Hf^{4+}	0.81	270
Sm^{3+}	0.97	317	Zr^{4+}	0.80	269

[a] Superposing structure [1b].

Procedure

For the synthesis of compounds which show no indication of second phases from X-ray diffraction the carefully purified starting materials thallium iodide, an iodide of element M, and iodine were transferred in stoichiometric amounts to a quartz ampule, which was cooled with liquid nitrogen and then sealed under vacuum. An excess of iodine was necessary for compensation of the free volume. The mixture of reactants was heated until molten, the ampule shaken and then quenched in water. Finally the ampule was allowed to stand for two to three weeks at a temperature just below the melting or decomposition temperature. Thus far, single crystals of the Ag, Au, Pb, and Bi compounds have been obtained by hydrothermal synthesis in hydriodic acid[5] and by the Bridgman method[6].

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CAS Registry numbers:
$Tl_6I_6Ag_2^+(I_4)^{2-}$, 67338-08-3; $Tl_6I_6Au_2^+(I_4)^{2-}$, 67338-07-2; $Tl_6I_6Pb^{2+}(I_4)^{2-}$, 59709-98-7; $Tl_6I_6Bi_{2/3}^{3+}(I_4)^{2-}$, 67338-06-1; $Tl_6I_6La_{2/3}^{3+}(I_4)^{2-}$, 67338-03-8; $Tl_6I_6Pr_{2/3}^{3+}(I_4)^{2-}$, 67338-01-6; $Tl_6I_6Nd_{2/3}^{3+}(I_4)^{2-}$, 67338-02-7; $Tl_6I_6Sm_{2/3}^{3+}(I_4)^{2-}$, 67338-00-5; $Tl_6I_6Fu^{2+}$, $(I_4)^{2-}$, 67338-05-0; $Tl_6I_6Th_{1/2}^{4+}(I_4)^{2-}$, 67337-99-9; $Tl_6I_6Hf_{1/2}^{4+}(I_4)^{2-}$, 67338-04-9; $Tl_6I_6Zr_{1/2}^{4+}(I_4)^{2-}$, 67337-98-8

[1] a) *A. Rabenau, H. Schulz, W. Stoeger*, Naturwissenschaften *63*, 245 (1976); b) *W. Stoeger, H. Schulz, A. Rabenau*, Z. Anorg. Allg. Chem. *432*, 5 (1977).
[2] *K. F. Tebbe*, 24th IUPAC-Congress Hamburg 1973, Abstracts, p. 346; Habilitationsschrift; Universität Münster 1975.
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[7] This structural type has also been observed for cerium and the heavy lanthanoids gadolinium, terbium, dysprosium and erbium, and yttrium: *G. Trageser*, unpublished.

An Organotitanium Compound with Ylide Clamps between Two Octahedrally Coordinated Metal Atoms[**]

By *Wolfgang Scharf, Dietmar Neugebauer, Ulrich Schubert,* and *Hubert Schmidbaur*[*]

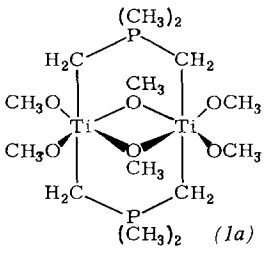
Organometallic compounds derived from phosphorus ylides are of topical interest owing to their novel structural and bonding features[1] and their potential use in homogeneous catalysis[2]. Derivatives of such compounds with titanium as the central metal atom, which are especially promising in this connection, are so far limited to only a few examples[2a, 3]. We report here on the synthesis and structural characterization of a binuclear titanium compound, for which there is no precedent in the coordination chemistry of ylides.

Reaction of methoxytitanium halides with (trimethylphosphonio)methylide in ether, even in non-stoichiometric amounts, leads with redistribution of the methoxy groups to a yellow crystalline product of the composition $(CH_3O)_6Ti_2[(CH_2)_2P(CH_3)_2]_2$ *(1)*. At the same time, tetramethylphosphonium halide is formed as a by-product of the transylidation according to the idealized equation:

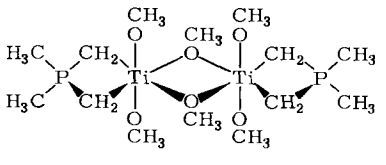
$$2(CH_3O)_3TiCl + 4(CH_3)_3P{=}CH_2 \rightarrow 2[(CH_3)_4P]Cl + (1)$$

$(CH_3O)_3TiCl$, $(CH_3O)_2TiCl_2$ *etc.* react very similarly, thus indicating an unusually high tendency for formation of *(1)*, m.p. 93–95 °C (dec.); the formula of the binuclear complex is confirmed by elemental analysis and the mass spectrum ($M^+ - OCH_3$, $m/e = 430$).

From the spectroscopic data two alternative highly symmetrical structures *(1a)* and *(1b)* are plausible. Two singlets (area ratio 2:1) are observed for the methoxy groups, both in the ^{1}H-NMR spectrum ($\delta CH_3O = 4.45$ and 4.28) and in the ^{13}C-NMR spectrum ($\delta CH_3O = 62.09$ and 59.18) as well as two doublets in each case for each of the alkyl groups on phosphorus [$\delta CH_3P = 1.03$, d, 6H, $^2J(PCH) = 12.0$ Hz; $\delta CH_2P = 0.45$, d, 4H, $^2J(PCH) = 13.5$ Hz and $\delta CH_3P = 20.72$, d, 2C, $^1J(PC) = 32$ Hz; $\delta CH_2P = 18.73$, d, 2C, $^1J(PC) = 39$ Hz, respectively]. The $^1H\{^{31}P\}$-experiment gives s(6H), s(3H), s(6H), s(4H) and the $^{31}P\{^1H\}$-spectrum shows a sharp singlet ($\delta P = 26.56$).



(1a)

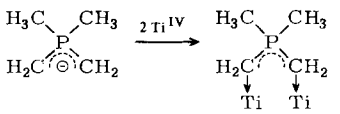


(1b)

Only the X-ray structure analysis[4] shows unequivocally that the complex does not have the chelate structure *(1b)*, for which there are numerous examples in the case of other metals[1, 5], but the novel structure *(1a)* with ylide-bridging of the coordination octahedra.

Noteworthy are the remarkably long Ti—C σ-bonds (cf. Fig. 1 and *e.g.* [6]), while at the same time the P—CH_2 bond lengths are so short that the bridge ligand has, at least in part, preserved its ylidic nature.

Consistent with this finding is the high chemical reactivity of this sensitive compound.



The Ti—Ti distance (325 pm) infers that there are hardly any bonding interactions between the metal atoms. Bridge and terminal Ti—O distances are expectedly very different. The folding of the formal $P_2C_4Ti_2$ eight-membered ring is the same as that observed in the analogous copper[7] and gold complexes[8], in which, however, the metal atoms are not six-coordinated but only two-coordinated.

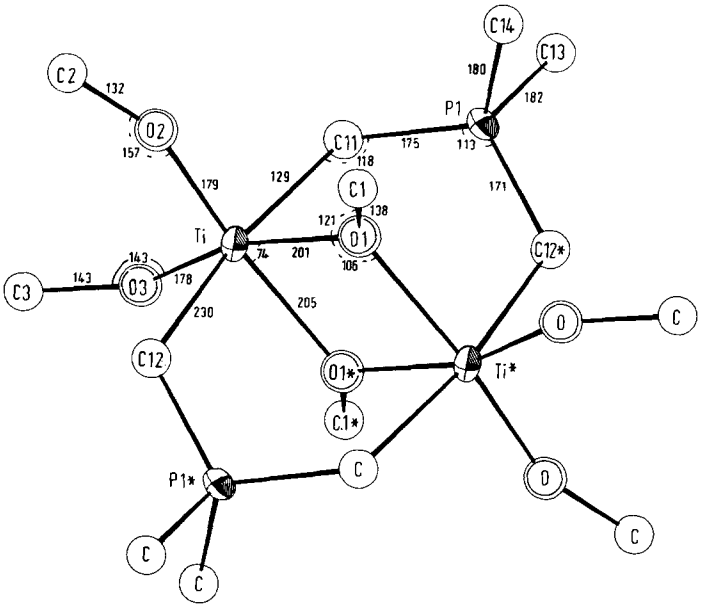


Fig. 1. Structure of complex *(1)* in the crystal, with bond lengths [pm], bond angles [°].

Procedure

To a solution of dichlorodimethoxo- or chlorotrimethoxotitanium in diethyl ether at room temperature is added an excess of (trimethylphosphino)methylide [molar ratio ≥ 1:2]. After one hours' stirring the reaction mixture is filtered and the filtrate evaporated down almost to complete dryness and allowed to crystallize at −20 °C. Recrystallization from toluene affords yellow crystals of *(1)* in 20—60 % yield.

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$(CH_3O)_3TiCl$, 3981-89-3; $(CH_3)_3P{=}CH_2$, 14580-91-7, *(1a)*, 67254-44-8

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[4] 1046 structural factors ($I \geq 3.5\sigma$, Syntex $P2_1/XTL$ $3° \leq 2\theta \leq 42°$), $R_1 = 0.082$; triclinic, space group $P\bar{1}$, $a = 860(1)$, $b = 968(1)$,

$c = 1448(3)$ ppm; $\alpha = 103.22(14)$, $\beta = 92.02(13)$, $\gamma = 93.77(14)°$, $V = 1169 \times 10^6$ pm^3. The unit cell contains two crystallographically independent molecules, each having C_i symmetry.

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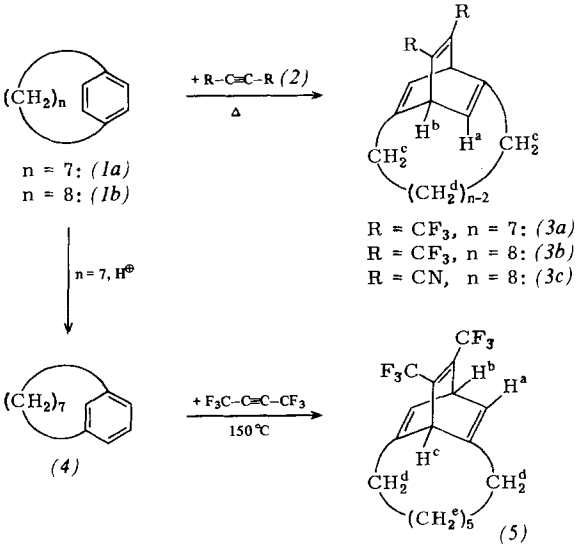
Cycloadditions with [*n*]Cyclophanes[1]

By *Karl-Ludwig Noble, Henning Hopf, Maitland Jones, Jr.*, and *Seetha L. Kammula*[*]

Benzene and its simple derivatives generally do not tend to play the role of the diene component in Diels-Alder reactions[2]. However, this passive nature can occasionally be overcome by drastic experimental conditions, Lewis acid catalysis, or by the use of strong dienophiles such as dicyanoacetylene, perfluoro-2-butyne, or tetrafluorodehydrobenzene[3].

Another possibility of increasing reactivity consists in the use of sterically strained arenes. Thus, *e.g.* [2.2]paracyclophane (strain energy *ca.* 31 kcal/mol) reacts with dicyanoacetylene[3a] and with tetrafluorodehydrobenzene[3c] to give 1:1 and 1:2 adducts. No cycloaddition takes place with the less reactive dimethyl acetylenedicarboxylate; however, this dienophile does add to the more highly strained [2.2.2](1,2,4)cyclophane (170 °C, 1 h, 61 %)[4].

Since [*n*]cyclophanes with small numbers of bridging members have become readily accessible recently[5], the question of their behavior in [2+4] cycloadditions has attracted interest. We report here on the Diels-Alder reactions of [7]-*(1a)* and [8]paracyclophane *(1b)* and of [7]metacyclophane *(4)*.



The hydrocarbons *(1a)* and *(1b)* react with an excess of perfluorobutyne *(2)*, R = CF_3, on heating to 160 °C for 3 h to give 1:1 adducts (MS analysis) in 52 and 12.5 % yield, respectively, whose structures *(3a)* and *(3b)* follow from spectroscopic data. The ^{1}H-NMR spectra of these bridged barrelenes are highly informative[6]. In the more complex spectrum ($CDCl_3$) of the solid *(3b)* (m.p. 53 °C) the olefin protons H^a appear as a pseudo double-doublet at $\delta = 6.45$ (2H, $J_1 = 6.0$, $J_2 = 2.0$ Hz, coupling with H^c no longer resolved), the bridgehead protons H^b as a sharp double doublet at 4.59 (2H, $J_1 = 6.0$, $J_2 = 2.0$ Hz), the methylene protons H^c at 2.25 (4H, ps-t, $J = 6.5$ Hz) and the remaining bridge protons as an unstructured multiplet between 1.7 and 0.8 (12H). For the oily adduct *(3a)* the corresponding signals are observed at $\delta = 6.52$ (2H, ps-d, $J = 5.5$ Hz, H^a), 4.64 (2H, dd, $J_1 = 5.5$, $J_2 = 1.5$ Hz, H^b), 2.24 (4H, m, H^c) and 1.26 (10H, m, H^d). If the reaction time is prolonged to 24 h in the case of *(1b)*, the yield of *(3b)* increases to 76.5 %. The shorter-bridged phane thus proves to be more suitable for addition; this can be explained in terms of its higher strain energy in comparison to *(1b)*[7]. Under comparable conditions (*o*-dichlorobenzene, 170 °C, 24 h), dicyanoacetylene *(2)*, R = CN, does not react with *(1b)*; cycloaddition to the solid *(3c)* (m.p. 186 °C) [24.6 %; NMR[6] ($CDCl_3$): $\delta = 6.45$ (2H, ps-dd, $J_1 = 2.0$ Hz, H^a), 4.58 (2H, dd, $J_1 = 6.0$, $J_2 = 2.0$ Hz, H^b), 2.27 (4H, ps-t, $J = 7.0$ Hz, H^c), 0.8—1.7 (12H, m, H^d)] takes place only on addition of aluminum trichloride (*o*-dichlorobenzene, 120 °C, 24 h). Finally since dimethyl acetylenedicarboxylate *(2)*, R = $COOCH_3$, does not add to *(1b)*, even with this type of activation ($AlCl_3$/*o*-dichlorobenzene, 120 °C, 24 h) the dienophilicity of the triple bond dienophiles *(2)* towards the arenes *(1)* decreases along the series R = $CF_3 > CN \gg COOCH_3$.

If *(1a)* is treated with a mixture of fluorosulfonic acid and *p*-toluenesulfonic acid in benzene, it isomerizes to the [7]metacyclophane *(4)*. This hydrocarbon also reacts with perfluorobutyne at 150 °C to give an oily 1:1 adduct (50 %), which according to spectroscopic analysis is the isomer *(5)* of *(3a)* [NMR[6] ($CDCl_3$): $\delta = 6.28$ (2H, d, $J = 6.0$ Hz, H^a), 4.82 (2H, t, $J = 6.0$ Hz, H^b), 4.72 (2H, ps-s, H^c), 2.30 (4H, m, H^d), 1.37 (10H, m, H^e)]. As shown by all the above additions the passive nature of benzene rings towards dienophiles can also be overcome by bridging with a relatively short polymethylene chain. Furthermore, the adducts *(3a—c)* and *(5)* are of interest for photoisomerization studies, since their parent compound barrelene may be photorearranged to semibullvalene and cyclooctatetraene[8].

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[6] The remaining spectroscopic data are given in the complete work.

[7] Calculated strain energy of [8]paracyclophane = 16.8 kcal/mol, that of [7]paracyclophane = 20.9 kcal/mol: *N. L. Allinger, J. T. Sprague, T. Liljefors*, J. Am. Chem. Soc. *96*, 5100 (1974). *Note added in proof* (July 22, 1978): Recent MNDO calculations by *Schweig et al.* yield distinctly higher strain energies for [*n*]paracyclophanes; *ie.g.* 31.9 instead of 20.9 kcal/mol for *(1a)*: *A. Schweig, H. Schmidt, W. Thiel, M. Jones, Jr.*, Chem. Ber. *111*, 1958 (1978).

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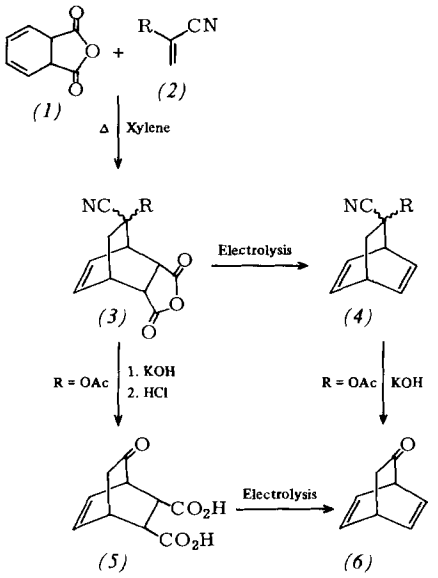
Bicyclo[2.2.2]octa-5,7-dien-2-one ("Barrelenone")[**]

By *Rudolf Gompper* and *Karl-Heinz Etzbach*[*]

Polar substituents influence the reactive behavior of ambifunctional anions and cations by inducing an alteration in charge distribution (allopolarization principle[1]). The aromaticity of a ring system can also alter the polarity and reactivity of an ambifunctional system. The same would appear to apply for bicycloaromaticity: reaction of the anion of bicyclo[4.2.2]-decatrienone with dimethyl sulfate[2] gives a remarkably high yield of enol ether (*O*-methylation).

In continuation of our investigations on the alkylation of the dibenzobarrelenone anion (predominantly *C*-methylation, cf. [1]), we have therefore synthesized bicyclo[2.2.2]octa-5,7-dien-2-one *(6)* in order to study the alkylation of its anion bicyclo[2.2.2]octa-2,5,7-trien-2-olate.

On heating dihydrophthalic anhydride *(1)* (prepared from dihydrophthalic acid and acetic anhydride) with the acrylonitriles *(2a)* and *(2b)* (for the use of *(2)* as ketone equivalent cf. [3]), 7-acetoxy-7-cyanobicyclo[2.2.2]octa-5-ene-2,3-dicarboxylic anhydride *(3a)* (45%, yellow, amorphous powder) and the 7-chloro analog *(3b)* (50%, colorless powder, m.p. 159—161 °C (from chloroform) are obtained, respectively.

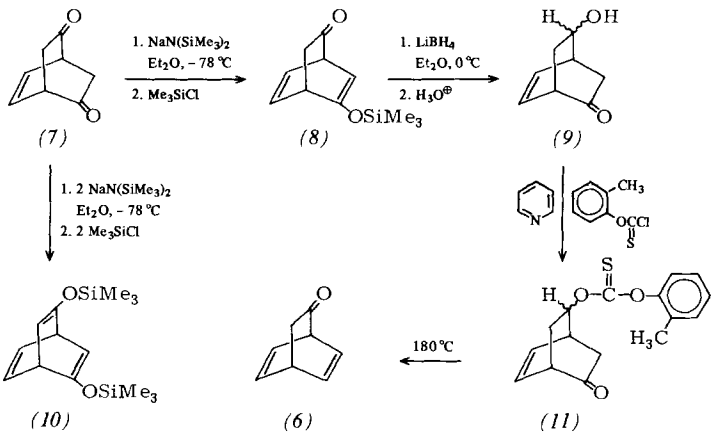


(a), R = OAc; *(b)*, R = Cl

Electrolysis of *(3a)* and of *(3b)* (pyridine/triethylamine/water, 90 V, 0.6—0.4 A, room temperature 7 h; cf.[4]) leads to 7-acetoxy-7-cyanobicyclo[2.2.2]octa-2,5-diene *(4a)* (*ca.* 20%; colorless oil, b.p. 100 °C/0.01 mbar (bulb-to-bulb dist.) and the 7-chloro analog *(4b)* (25—30%; colorless needles (from ether) m.p. 62—64 °C), respectively.

Alkaline hydrolysis of *(3a)* yields the dicarboxylic acid *(5)* (70%, colorless, amorphous powder). Both electrolysis of *(5)* (22% yield) as well as alkaline hydrolysis of *(4a)* (70% yield) then afford the barrelenone *(6)* (colorless oil, b.p. 90 °C/17 mbar (bulb-to-bulb dist.); ^{1}H-NMR ($CDCl_3$): $\delta = 1.86$ (d, $J = 3$ Hz; 2H, CH_2), 3.76—4.32 (m; 2H, CH), 6.60 (mc; 4H, —CH=); IR (film): 3065, 2990, 2923, 1725, 1615, 1580 cm^{-1}; 2,4-dinitrophenylhydrazone: red needles m.p. 183—184 °C (from ethanol)).

A second route to *(6)* starts from bicyclo[2.2.2]oct-7-ene-2,5-dione *(7)*[5]. Reaction of *(7)* with Na-bis(trimethylsilyl)-amide in ether at −78 °C affords the Na-salt, which reacts



with trimethylchlorosilane to give the barrelenone derivative 5-trimethylsiloxybicyclo[2.2.2]octa-5,7-dien-2-one *(8)* (75—80%; colorless oil, b.p. 119 °C/17 mbar). Reaction of the disodium salt of *(7)* with trimethylchlorosilane yields 2,5-bis-(trimethylsiloxy)bicyclo[2.2.2]triene *(10)*, a new barrelene derivative (70%, colorless oil). Reaction of *(8)* with $LiBH_4$ and acid hydrolysis of the reaction mixture affords 8-hydroxybicyclo[2.2.2]oct-5-en-2-one *(9)* (68%, colorless needles (from ether/hexane), m.p. 150—155 °C). *(9)* can be converted by known methods[5] into the thiocarbonate *(11)* (99%; yellow-red oil) whose subsequent thermolysis (180 °C/17 mbar) likewise affords barrelenone *(6)* in 70% yield.

Table 1. Methylation of the Na-salts [a] of bicyclic ketones with methyl fluorosulfate in the presence of [18]-crown-6 at 78 °C in ether.

Ketone	$P_{O/C} = l_O/l_C$ [b]	Q_O/Q_C [c]
Barrelenone *(6)*	1.63	0.05
Benzobarrelenone *(12)*	2.02	0.10
Dibenzobarrelenone *(13)*	2.33	0.35
Dihydrobarrelenone *(14)*	2.06	0.53
Dihydrobenzobarrelenone *(15)*	2.39	0.87
Tetrahydrobarrelenone *(16)*	2.78 [d]	1.90

[a] Prepared with $NaN[Si(CH_3)_3]_2$ in Et_2O at −78 °C.
[b] l = HMO charge, calculated with $h_O = 1.0$, $k_{CC} = k_{CO} = 1.0$, homoconjugation $k_{CC} = \pm 0.5$.
[c] Yield ratio % *O*-methylation to % *C*-methylation.
[d] Calculated for the anion of 2-butanone.

The course of methylation of Na-salt of *(6)* and other bicyclic ketones proceeds according to predictions based on the allopolarization principle: As can be seen from Table 1 the tendency towards *O*-methylation also increases with increasing polarity index $P_{O/C}$ in the series[6]

(6), (12), (13); (6), (14), (16); (14), (15)

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CAS Registry numbers:
(1), 85-44-9; *(2a)*, 3061-65-2; *(2b)*, 920-37-6; *(3a)*, 67209-47-6; *(3b)*, 67209-48-7; *(4a)*, 67209-49-8; *(4b)*, 67209-50-1; *(5)*, 67209-51-2; *(6)*, 67209-52-3; *(6)*, 2,4-DNPH, 67209-53-4; *(6)*, Na salt, 67209-54-5; *(6)*, *O*-methylation, 67209-55-6; *(6)*, *C*-methylation, 67209-56-7; *(7)*, 17660-74-1;

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(7), di-Na salt, 67209-57-8; *(8)*, 67209-58-9; *(9)*, 67209-59-0; *(10)*, 67209-60-3; *(11)*, 67209-61-4; *(12)* Na salt, 67209-62-5; *(12)* *O*-methylation, 67209-63-6; *(12)*, *C*-methylation, 67209-64-7; *(13)*, Na salt, 67209-65-8; *(13)*, *O*-methylation, 67209-66-9; *(13)*, *C*-methylation, 67209-67-0; *(14)*, Na salt, 67209-68-1; *(14)*, *O*-methylation, 67209-69-2; *(14)*, *C*-methylation, 67209-70-5; *(15)*, Na salt, 67209-71-6; *(15)*, *O*-methylation, 67209-72-7; *(15)*, *C*-methylation, 67209-73-8; *(16)*, Na salt, 67209-74-9; *(16)*, *O*-methylation, 67209-75-0; *(16)*, *C*-methylation, 67209-76-1; Na-bis(trimethylsilyl)-amide, 1070-89-9; trimethylchlorosilane, 75-77-4

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[6] *Note added in proof* (July 11, 1978): Presented in part at the "Third International Symposium on Novel Aromatic Compounds" at San Francisco, August 22—26, 1977 (cf. Abstr. of Papers).—Meanwhile, *H. Prinzbach, H.-P. Schal*, and *D. Hunkler* (Tetrahedron Lett. *1978*, 2195) have mentioned a further mode of formation of *(6)*.

Synthesis and Properties of Tris(trimethylgermyl)aluminum[**]

By *Lutz Rösch* and *Wolfgang Erb*[*]

Organoaluminum compounds are well known and are of considerable preparative interest. In contrast, very few analogs with germanium replacing carbon have so far been described. $R_3Ge—AlR_2$ has been postulated as an intermediate in the reaction of germanium halides with alkylaluminum derivatives[1], and *Calas* and co-workers recently isolated the salt $Li^+[(C_6H_5)_3GeAlH_3]^-$ [2] in the reaction of hexaphenyldigermane with lithium aluminum hydride.

We have now synthesized the first alkylgermylaluminum compound by reaction of bis(trimethylgermyl)mercury with aluminum:

$$3\,Hg[Ge(CH_3)_3]_2 + 2\,Al \xrightarrow{THF/Pentane} 2\,Al[Ge(CH_3)_3]_3 \cdot THF + 3\,Hg$$

The colorless, crystalline tetrahydrofuran adduct *(1)* ignites spontaneously in air; its decomposition in water or D_2O leads to formation of trimethylgermane or trimethyldeuteriogermane, respectively.

The new compound *(1)* is readily soluble in organic solvents such as ether, benzene, or pentane. The ^{1}H-NMR spectrum (benzene) shows only one additional sharp signal in the TMS region besides the coordinated tetrahydrofuran, as well as the ^{13}C-NMR spectrum which shows only one signal for the trimethylgermyl group at $\delta = 1.18$. The structure of *(1)* is confirmed by elemental analysis and the mass spectrum (molecular ion with expected isotopic satellites). *(1)* has an astonishingly high thermal stability; it melts without decomposition at 81 °C, but at 10^{-5} torr it loses part of the coordinated solvent at this temperature. The ^{1}H-NMR spectrum of the residue shows a broad signal in the TMS region. Hydrolysis affords trimethylgermane together with methane, which can be detected by IR spectroscopy. This would indicate decomposition with formation of dimethylgermanediyl, corresponding to the mode of decomposition already observed in the case of the homologous silicon compound[3].

$$Al[Ge(CH_3)_3]_3 \cdot THF \xrightarrow{81\,°C/10^{-5}\,torr} \{Al[Ge(CH_3)_3]_3\} + THF$$
$$\downarrow$$
$$CH_3Al[Ge(CH_3)_3]_2 + \{Ge(CH_3)_2\}$$

Isolation of the intermediary solvent-free tris(trimethylgermyl)aluminum is not possible under these conditions.

Attempts to prepare the likewise unknown tin compound *(2)* in an analogous way showed that *(2)* already decomposes below room temperature.

$$Al[Sn(CH_3)_3 \cdot THF \quad (2)$$

On reaction of bis(trimethylstannyl)mercury with aluminum the solution instantaneously decolorizes. During workup a colorless solid is obtained which contains tin as well as aluminum, but no mercury, and which ignites spontaneously in air. Hydrolysis leads to formation of trimethylstannane and methane. The ^{1}H-NMR spectrum shows a broad multiply split signal in the TMS region, thus indicating spontaneous decomposition of the initially formed tris(trimethylstannyl)aluminum with loss of dimethylstannanediyl under such reaction conditions. This instability in comparison to the germanium compound is consistent with the properties of the corresponding mercury compounds. Bis(trimethylgermyl)mercury is stable up to 120 °C[4], bis(trimethylstannyl)mercury decomposes at −10 °C[5].

Procedure

5 g $(Me_3Ge)_2Hg$ is dissolved in 50 ml pentane and 2 ml THF and stirred together with 8 g aluminum powder under argon until disappearance of the green color (*ca.* 24 h). The solution is filtered through a glass frit and the readily volatile components removed in an oil-pump vacuum at room temperature. The residue is recrystallized twice from a little pentane at −78 °C. 3.86 g (80 %) $Al[Ge(CH_3)_3]_3 \cdot THF$ is obtained as a white crystalline powder.

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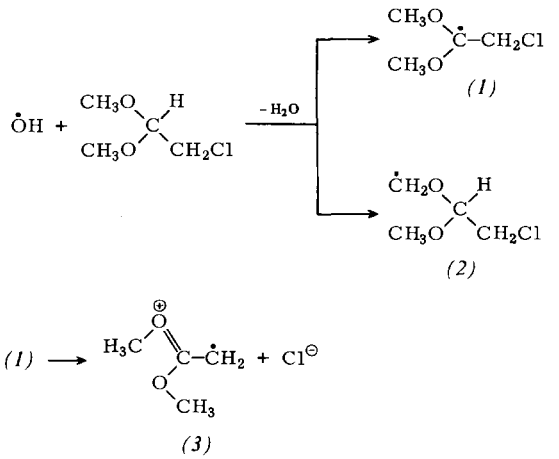
Evidence for a Dialkoxyalkene Radical Cation in Aqueous Solution

By *Günter Behrens, Eberhard Bothe, Johann Eibenberger, Günther Koltzenburg*, and *Dietrich Schulte-Frohlinde*[*]

In connection with our investigations on the radiation damage of DNA[1] we were interested in the elimination of phosphoric acid from β-phosphatoalkyl radicals[2]. As model species for our studies we used the 1-methoxy-2-phosphatoethyl radical, which rapidly loses phosphate in aqueous solution ($k = 3 \times 10^6\,s^{-1}$) and is converted into $CH_3O—\dot{C}H—CH_2OH$ and $CH_3O—CH(OH)—\dot{C}H_2$[2]. An analogous reaction in which chloride instead of phosphate is eliminated

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has been reported by *Norman et al.*[3], but no experimental evidence for formation of the postulated intermediary radical cation $CH_3\overset{\oplus}{O}{=}CH{-}\dot{C}H_2$ was given. We have now been able to demonstrate such an elimination reaction for the first time: $Cl^{\ominus}$-cleavage from the radical $(CH_3O)_2\dot{C}{-}CH_2Cl$ *(1)* leads directly to the 1,1-dimethoxyethylene radical cation *(3)*.



$\dot{O}H(SO_4^{\ominus})$ radicals, generated by irradiation of aqueous solutions of H_2O_2 (or $Na_2S_2O_8$), react with 2,2-dimethoxyethyl chloride to give the radicals *(1)* and *(2)* in approximately equal yields. Owing to its short lifetime (pulse conductivity measurements $<5\,\mu s$) *(1)* cannot be observed; it decomposes into $Cl^{\ominus}$ and the radical cation *(3)*, which does not react with water during the observation period of a few milliseconds. *(3)* is represented by only one canonical form in the formula scheme. The radical character and structure of *(3)* were determined ESR spectroscopically, and the charge by pulse conductivity measurements.

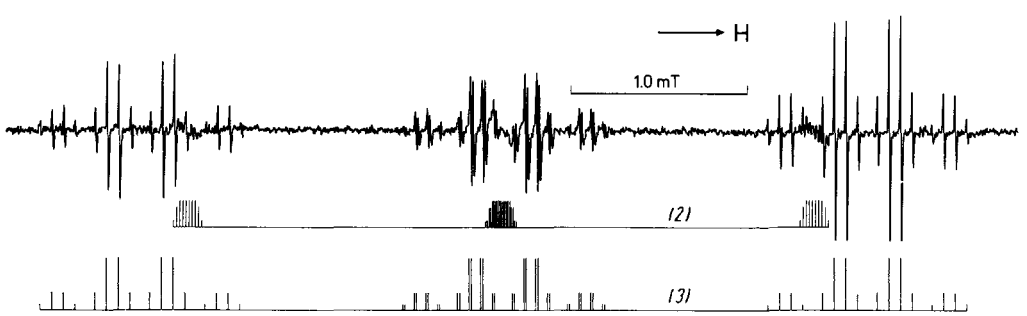


Fig. 1. ESR spectra of the radical cation *(3)* and the radical *(2)* at 276 K, measured during the UV irradiation of an aqueous solution (pH = 3.6) of 0.3 M acetone, 0.2 M 2,2-dimethoxyethyl chloride and 1.0×10^{-2} M peroxodisulfate. The spectrum of *(3)* consists of a triplet of two different quartets. The small doublet splitting of the central group (12.6 μT) arises from second-order effects. The lines of the central group appear somewhat broadened. This points to a small barrier to rotation about the C—C bond, resembling that in the case of ester radicals of the type $\dot{C}H_2{-}C(O)OCH_3$.

As also determined by time-dependent conductivity measurements, the radical cation *(3)* disappears bimolecularly ($2k = 2.5\times10^9$ l/mol·s) with subsequent addition of water and loss of a proton. The ESR spectrum [$a^{CH_{2(2)}} = 2.055$, $a_1^{OCH_{3(3)}} = 0.310$, $a_2^{OCH_{3(3)}} = 0.066$ mT; $g = 2.00306$] indicates the absence of chlorine and a high density of the positive charge on the oxygen atoms. The non-equivalence of the two methoxy groups indicates a difference in solvation and charge. An unsymmetrical spin- and charge-distribution has already been observed by *Symons et al.*[4] with *m*-dinitrobenzene radical anions and ascribed to a difference in solvation of the two nitro groups. According to thermochemical estimations an oxiranium structure for the radical cation *(3)* is less likely. The isomeric 1,2-dimethoxyethylene radical cation, prepared by reaction of $SO_4^{\ominus}$ with 1,2-dimethoxyethylene, is not observable ESR spectroscopically in water. On the other hand, radical cations of methoxybenzenes have already been observed in aqueous solution[5].

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The Formation of Stereoisomeric (η^2-Aroyl)arylbis(η^5-cyclopentadienyl)zirconium(IV) Compounds[**]

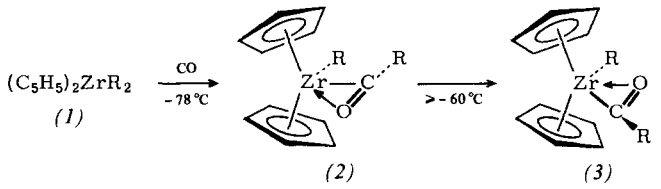
By *Gerhard Erker* and *Frank Rosenfeldt*[*]

The problem of the mechanism of "insertion" of carbon monoxide into transition metal-carbon σ-bonds has stimulated extensive investigations owing to the key role of this reaction step in important catalytic processes[1]. The assumption of intermediary η^2-acyl complexes in the reactions is implied by the independent synthesis and isolation of such acyl complexes. Their description as η^2-acyl complexes follows from the structural determination or from the IR spectra [$\nu_{C=O}(acyl) < 1600\,cm^{-1}$][2]. We have now obtained new results on the stereochemistry of η^2-acyl complexes in the carbonylation of diarylbis(η^5-cyclopentadienyl)zirconium(IV) compounds *(1)*.

The stereoisomeric η^2-acyl compounds *(2)* and *(3)* ought to be obtainable by carbonylation of the compounds *(1)*[3]. However, according to *Floriani* the carbonylation of *(1)* at room temperature leads to a uniform product, which can be assigned the structure *(3)*[4].

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(a), R = C_6H_5; *(b)*, R = *p*-CH_3—C_6H_4

On reaction of *(1)* with CO at −78 °C we obtained a carbonylation product that was different from *(3)*. With bromine at −78 °C this afforded the same degradation products as *(3)*: aryl bromide, aroyl bromide, and Cp_2ZrBr_2. A comparison of the spectral properties (Table 1) indicates a stereoisomer of *(3)*. The unusual position of the CO stretching vibration band in the IR spectrum and the absorption of the acyl carbon in the ^{13}C-NMR spectrum at remarkably low field[5] indicate the presence of a η^2-aroyl ligand in this complex. On the basis of these data and the isomerization to *(3)* we ascribe the structure *(2)* to the product.

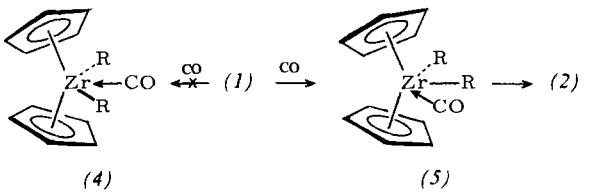
Table 1. Comparison of spectroscopic data of the stereoisomeric bis(η^5-cyclopentadienyl)*p*-toluoyl(*p*-tolyl)zirconium(IV) complexes *(2b)* and *(3b)*.

	(2b)	*(3b)*		
^{1}H-NMR (60 MHz, [D_8]-toluene, rel. to TMS), δ values, −68 °C)	5.57	5.28	(10H)s	$2C_5H_5$
	1.90	2.01	(3H)s	*p*-CH_3—C_6H_4
	6.8 (ν_A), 7.7 (ν_B)	6.8 (ν_A), 7.8 (ν_B)	(4H)AA'BB'	
	2.45	2.48	(3H)s	*p*-CH_3—C_6H_4—CO
	7.2 (ν_A), 8.2 (ν_B)	7.3 (ν_A), 8.3 (ν_B)	(4H)AA'BB'	
^{13}C-NMR (CD_2Cl_2/$CDCl_3$ 3:2, rel. to TMS, δ-values, −75 °C)	300	301	acyl carbon	
IR (CH_2Cl_2, −78 °C)	1480 cm^{-1} [a]	1505 cm^{-1}	$\nu_{C=O}$ (acyl)	

[a] Bands expected for a bent metallocene were also observed; *H. P. Fritz*, Adv. Organomet. Chem. *1*, 262 (1964).

When the solution of *(2)* obtained at −78 °C is allowed to warm to −60 °C, formation of *(3)* is observed (^{1}H-, ^{13}C-NMR, IR). This rearrangement proceeds intramolecularly. Crossover experiments with addition of *(1a)* to a solution of *(2b)* provide no indication of CO transfer; an exchange of aryl groups does not take place. The rearrangement is not reversible. The rates of rearrangement of *(2a)* to *(3a)* and of *(2b)* to *(3b)* were determined ^{1}H-NMR spectroscopically at −59 °C. The reactions can be described in terms of a first-order rate law with Gibbs activation energies of $\Delta G^{\neq}_{59\,°C} = 63.5 \pm 4.7$ [kJ/mol] and 65.2 ± 3.9 [kJ/mol], respectively[6].

It follows from these results that in the investigation of the stereochemistry of CO-insertion reactions the possibility of isomerization—and thus the loss or inversion of stereochemical information—at the stage of a η^2-acyl intermediate must not be ignored. The kinetically controlled, stereospecific



(4) *(5)*

formation of *(2)* in the reaction of *(1)* with CO would suggest that the CO coordination formulated as the initial step does not, as has repeatedly been postulated[4a, 4c, 7], take place at the central position between the two σ-bonded ligands to give *(4)*[8] but, in accordance with calculations by *Hoffmann*[9a] and spectroscopic investigations by *Dahl*[9b], *via* a further route to the product *(5)*.

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[5] The metal-carbene character of the metal-(η^2-acyl)carbon bond [4a] deduced from the bond lengths is supported by these ^{13}C-NMR absorptions.
[6] Whether the isomerization *(2)* → *(3)* should be described in terms of a simple rotation of the η^2- acyl ligand, formulated as in the case of similar systems [*R. D. Adams, D. F. Chodosh*, Inorg. Chem. *17*, 41 (1978)], cannot be decided here.
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5-Methylenebicyclo[2.2.0]hex-2-ene, a Bicyclic Isomer of Toluene: Synthesis and Thermal Behavior[**]

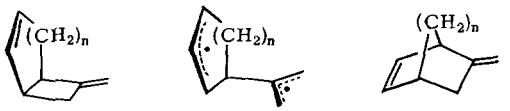
By *Dieter Hasselmann* and *Klaus Loosen*[*]

At temperatures around 200 °C the bicyclic methylenecycloalkenes *(1b)*[1a] and *(1c)*[1b] undergo both degenerate methylenecyclobutane rearrangement and structural isomerization to the methylenebicyclo[2.2.*n*]alkenes *(2b)* and *(2c)*, respectively. The energy parameters of these rearrangements

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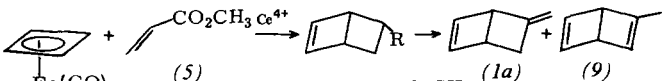
and the results of stereochemical investigations on *(1b)*[2] suggest participation of non-equilibrating diradicals *(3b)* and *(3c)*, respectively. The ratio of degenerate to structural isomerization in *(1b)* and *(1c)*, however, is strongly influenced by conformational effects[1].



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

(a), n = 0; *(b)*, n = 1; *(c)*, n = 2

Such effects should be minimal in the bisallyl diradical *(3a)* with C_s symmetry. As the first stage in our studies on *(3a)* we report here on the synthesis and behavior of 5-methylenebicyclo[2.2.0]hex-2-ene *(1a)* [≡*(2a)*]. This compound is of topical interest, not only as a bicyclic isomer of toluene, but also as a precursor of 5-methylene-1,3-cyclohexadiene *(13)*[3].



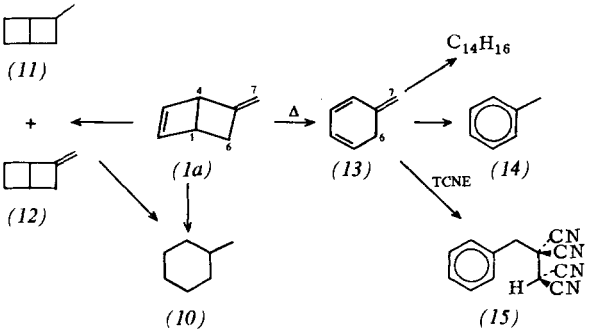
(4) *(5)* *(6)*, R = CO_2CH_3 *(1a)* *(9)*

(7), R = CH_2OH

(8), R = CH_2OTs

For the synthesis of *(1a)* we used as starting compound the ester *(6)*, which was obtained in 57% yield (*endo/exo* = 94/6) by oxidation of *(4)* with ammonium cerium(IV) nitrate in the presence of an excess of *(5)*[4]. Reduction with $LiAlH_4$ afforded the alcohol *(7)* as a viscous oil, which was esterified with *p*-toluenesulfonyl chloride in pyridine to the tosylate *(8)* (m.p. 39—40°C, 93%). Elimination with potassium *tert*-butoxide in DMSO (room temperature, 10^{-3} torr) led to two hydrocarbons (48%, 9:1) which were identified as *(1a)* and *(9)*[5]. Attempts to prepare *(1a)* directly by addition of allene to cyclobutadiene, generated from *(4)*, met without success. However, in the analogous reaction of *(4)* in the presence of propyne, *ca.* 15% *(9)* was formed.

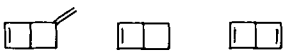
The structure of *(1a)*, isolated in pure form by PGC, followed from its spectral data[6], its hydrogenation (Pd/C) exclusively to methylcyclohexane *(10)*, its reduction with diimine with retention of the bicyclo[2.2.0]hexane structure to *(11)* and *(12)* (which are likewise hydrogenated (Pd/C) to *(10)*), its reaction with dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate with evolution of nitrogen to give the cyclobutene monoadduct[7], and its thermal behavior.



The thermolysis of *(1a)*, both under flow conditions in the gas phase up to 200°C as well as in solution, initially leads exclusively to *(13)*[3,8]. In the gas phase *(13)* isomerizes partially to toluene *(14)*, in solution it reacts—apparently in the sense of a formal ene reaction—with *(1a)* still present to give the (as yet only mass spectroscopically identified) dimers $C_{14}H_{16}$. In the presence of an excess of tetracyanoethylene (TCNE) these secondary reactions can be suppressed quantitatively in favor of the 3-phenyl-1,1,2,2-propanetetracarbonitrile *(15)*[5,9]. *(1a)* itself does not react with TCNE.

We have monitored the kinetics[10] of thermal ring opening of *(1a)* in the presence of TCNE in [D_8]-THF and in CD_3CN. The rate of disappearance of *(1a)* and formation of *(15)* in 2 to 7 M excess of TCNE is independent of concentration and is almost uninfluenced by the difference in solvent polarity ($k_{CD_3CN}/k_{[D_8]\text{-THF}} = 1.1$—$1.2$). The opening of the C^1C^4 bond in *(1a)* to give *(13)* is thus rate-determining: it is strictly a first-order reaction. The activation energy for the orbital symmetry-forbidden cyclodissociation of *(1a)* determined in each case at six temperatures between 35.0 and 60.0°C (Table 1) is reduced by the exocyclic methylene substituent by about 7—8 kcal/mol compared to that of the unsubstituted system *(16)*[11a-11c] and thus is only slightly higher than that of Dewar-benzene *(17)*[11d].

Table 1. Activation parameters of compounds *(1a)*, *(16)* and *(17)*.



(1a) *(16)* *(17)*

Cpd.		E_a [kcal/mol] [a]	log *A* [s^{-1}]	Ref.
(1a)	[D_8]-THF	25.11 ± 0.16 [b]	12.76 ± 0.11	
	CD_3CN	24.71 ± 0.22	12.56 ± 0.15	
(16)	Gas phase	31.9 ± 0.2	13.28	[11a]
	Gas phase	32.95 ± 0.09	13.87 ± 0.04	[11b]
	Solution	31.7	13.6	[11c]
(17)	C_2Cl_4	23.0 ($\Delta H^{\neq}$)	−5.0 ($\Delta S^{\neq}$)	[11d]

[a] 1 cal = 4.1868 J. [b] Standard deviation by method of least squares.

In contrast to *(1b)* and *(1c)*, in *(1a)* no competitive opening of the peripheral C^1C^6 bond with rupture of the central bond can be detected by deuterium labeling in the exocyclic methylene position [*via* reduction of *(6)* with $LiAlD_4$] even after 91% conversion to *(13)*, either in the reisolated starting material or in the end product *(15)*. As expected the generation of an allylcyclobutenyl diradical *(3a)* requires other precursors than the bicyclic toluene isomer *(1a)*.

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[1] a) *D. Hasselmann*, Tetrahedron Lett. *1972*, 3465; *1973*, 3739; b) *D. Hasselmann, P.-J. Rissing*, unpublished; *P.-J. Rissing*, Diplomarbeit and Dissertation, Universität Bochum, 1975 and 1978.

[2] *D. Hasselmann*, Angew. Chem. *87*, 252 (1975); Angew. Chem. Int. Ed. Engl. *14*, 257 (1975).

[3] Synthesis of *(13)*: a) *W. J. Bailey, R. A. Baylouney*, J. Org. Chem. *27*, 3476 (1962); b) *K. R. Kopecky, M.-P. Lau, ibid. 43*, 525 (1978); c) *W. A. Pryor, W. D. Graham, J. G. Green, ibid. 43*, 526 (1978); cf. also d) *W. A. Pryor, W. D. Graham, ibid. 43*, 770 (1978).

[4] *(6)* was previously obtained in only 3% yield by *McDonald et al.*: *R. N. McDonald, G. E. Davis*, J. Org. Chem. *34*, 1916 (1969); alternatively *(6)* is accessible by ring contraction starting from bicyclo[3.2.0]hept-6-en-2-one *via* 3-formylbicyclo[3.2.0]hept-6-en-2-one (64%), conversion into 3-diazobicyclo[3.2.0]hept-6-en-2-one (72%) and subsequent photolysis (Pyrex, Philips-HPK 125 W) in methanol (60%; *endo/exo* = 80/20) [5].

[5] The spectroscopic data of all the new substances are in agreement with the given structures.

[6] *(1a)*: ^{1}H-NMR (CCl_4): $\delta = 2.15$—3.05 (m, H^6_{endo}, H^6_{exo}), 3.32 (m, H^1), 3.77 (m, H^4), 4.82 (m, *Z*-H^7, *E*-H^7), 6.28 (m, H^2, H^3); ^{13}C-NMR ($CDCl_3$): $\delta = 32.7$ (t, C^6), 40.0 (d, C^1), 53.8 (d, C^4), 107.9 (t, C^7), 139.5, 142.1 (each d, C^2, C^3), 148.5 (s, C^5); IR (CCl_4): *inter alia* 3100 (=CH), 3070 (=CH), 3040 (=CH), 1668 (C=CH_2), 1547 (C=C), 880, 682 cm^{-1}; MS (70 eV): $m/e = 92$ (33 %, M^+), 91 (100 %).

[7] MS (70 eV): $m/e = 262$ (2 %, M^+), 91 (50 %), 66 (100 %); $C_{13}H_{14}N_2O_4$: $m/e = 262.0948$ (M^+) (calc. 262.0953); IR and ^{1}H-NMR spectra indicate an isomeric mixture following rearrangement to the hydrazone structure.

[8] *(13)* is likewise a product of the retro-Diels-Alder reaction of *(2c)*, and partially survives at $T > 350$ °C in the static system [1b]. *(13)* reacts in solution in the presence of oxygen to give benzyl hydroperoxide [^{1}H-NMR (CCl_4): $\delta = 4.95$ (s, 2H), 7.38 (s, 5H)] [1b]. *(13)*: ^{1}H-NMR (CCl_4): $\delta = 3.32$ (m, $2H^6$), 4.83 (m, $2H^7$), 5.55—6.28 (m, 4H); IR (CCl_4): *inter alia* 3080, 3040, 1598, 1408, 1010, 865, 650 cm^{-1}.

[9] *(15)*: ^{1}H-NMR ([D_8]-THF): $\delta = 3.62$ (s, 2H), 5.70 (s, 1H), 7.48 (s, 5H); (CD_3CN): $\delta = 3.60$ (s, 2H), 5.20 (s, 1H), 7.52 (s, 5H); *(15)* is identical with the comparison compound obtained in 73 % yield from benzylmagnesium chloride and TCNE after hydrolysis [1b], and does not correspond to the Diels-Alder adduct formulated in [3a]. An analogous ene product gives *(13)* with 4-phenyl-1,2,4-triazoline-3,5-dione [1b, 5].

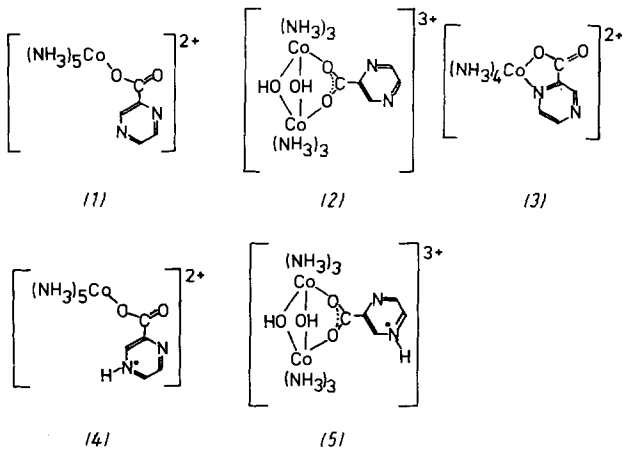
[10] Thermolyses were carried out in sealed NMR tubes in a thermostat (±0.05 °C); after quenching the ^{1}H-NMR spectra were recorded at *ca.* 0 °C.

[11] a) *G. Erker*, Dissertation, Universität Bochum 1973; b) *M. J. Goldstein, R. S. Leight, M. S. Lipton*, J. Am. Chem. Soc. *98*, 5717 (1976); c) *H.-D. Martin, M. Hekman*, Angew. Chem. *88*, 447 (1976); Angew. Chem. Int. Ed. Engl. *15*, 431 (1976); d) *R. Breslow, J. Napierski, A. H. Schmidt*, J. Am. Chem. Soc. *94*, 5906 (1972).

Intramolecular Electron Transfer of Coordinated Pyrazinecarboxylato Radicals to Cobalt(III): A Pulse Radiolytic Study[**]

By *Karl Wieghardt, Haim Cohen*, and *Dan Meyerstein*[*]

A possible "inner-sphere" mechanism for electron transfer (ET) between two redox-active metal centers through an organic bridging ligand proceeds *via* radical intermediates: an electron reduces the bridging ligand[1]. It is very difficult to obtain direct evidence for the occurrence of such radical species[2]. We have now been able to carry out the pulse radiolytic synthesis and characterization of the free radicals *(4)* and *(5)* for the first time, which have previously only been postulated as short-lived intermediates in the reduction of complexes *(1)* and *(2)* by Cr^{II}[2]. This is therefore regarded as direct demonstration of a "radical ion mechanism"[1] for electron transfer between metal ions.



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

(4) *(5)*

Upon irradiation with electrons (pulse intensity 800—3000 rad, 0.25—1 μs) of aqueous, 1 M isopropanol solutions saturated with N_2O (or Ar)[3], and containing the complexes *(1)* or *(2)* (1—10×10^{-5} mol/l), the formation of strongly absorbing species is observed. The absorption spectra are shown in Fig. 1. Under these conditions the isopropanol radical $(CH_3)_2\dot{C}$—OH reacts as electron transferring agent[3] with the complexes *(1)* and *(2)*, yielding acetone and the radicals *(4)* and *(5)* which are monoprotonated at the heterocyclic ring at pH > 3 (the actual site of protonation at the pyrazine ring is unknown):

$$(1) \text{ or } (2) + (CH_3)_2\dot{C}\text{—OH} \xrightarrow{k(4) \text{ or } k(5)} (4) \text{ or } (5) + (CH_3)_2C{=}O$$

The rate of formation of *(4)* and *(5)* is independent of pH (0—5) and pulse intensity, but dependent on the concentration of the complex[4].

The radicals *(4)* and *(5)* decompose intramolecularly according to a *first order* process with formation of one Co^{II} ion per radical cation; the decomposition is independent of the concentration of complex and the pulse intensity, but dependent on the pH (0—4) [Fig. 2]. The ratio of the $(CH_3)_2\dot{C}$—OH radicals produced by pulses to Co^{II} product is always 1:1; in contrast, the *p*-nitrobenzoato radical coordinated to Co^{III} disproportionates at high H^+ concentrations without formation of Co^{II}[3,6]. The doubly and singly protonated forms of *(4)* and *(5)* decompose at different rates[5]; the former have the longer lifetimes, they are formed at high

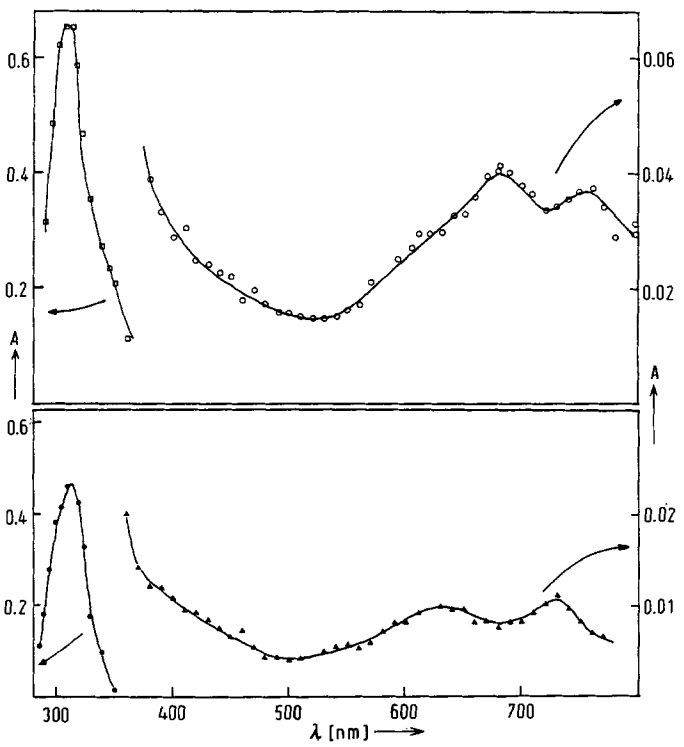


Fig. 1. Absorption spectra of fully protonated radical intermediates *(5)* (upper spectrum) and *(4)* (lower spectrum) at 22 °C. The spectra were recorded on solutions (Ar-saturated, 1 mol/l isopropanol, pH = 1) of the perchlorate salts of the complexes *(1)* and *(2)*.
□ $[(2)] = 2 \times 10^{-5}$ mol/l, pulse intensity 80 rad; ○ $[(2)] = 3 \times 10^{-4}$ mol/l, pulse intensity 860 rad; ● $[(1)] = 2 \times 10^{-5}$ mol/l, pulse intensity 80 rad; ▲ $[(1)] = 1 \times 10^{-4}$ mol/l, pulse intensity 800 rad.

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H^+ concentrations (pH < 2.7). The pK_a values could be determined "kinetically" from Figure 2 (2.7 for *(4)* and 2.6 for *(5)*); they are in good agreement with spectrophotometrically determined values.

$$Co^{III}—\dot{L}H_2 \overset{K_a}{\rightleftharpoons} Co^{III}—\dot{L}H + H^+$$

$$Co^{III}—\dot{L}H_2 \xrightarrow{k_d} Co^{II} + LH_2$$

$$Co^{III}—\dot{L}H \xrightarrow{k_p} Co^{II} + LH$$

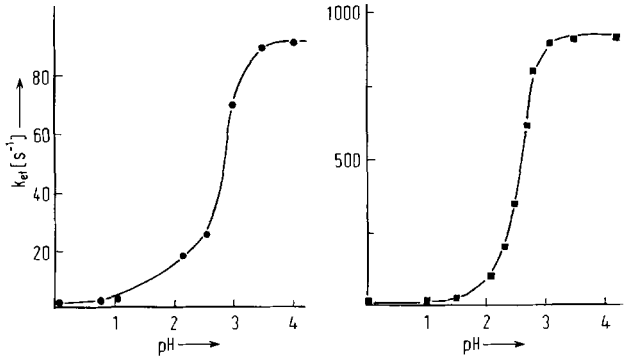


Fig. 2. Intramolecular ET rate constants, k_{et} [s^{-1}], of radicals *(4)* (left) and *(5)* (right) as a function of pH (22 °C).

(3) likewise reacts with $(CH_3)_2\dot{C}—OH$ with *direct* reduction of Co^{III} ($k = (9+2) \times 10^8$ l/mol·s, 22 °C, pH = 5) and *without* formation of a detectable radical intermediate. This indicates that the spin density of the radicals *(4)* and *(5)* is greatest at the N atoms of the aziridine ring. If one of these N atoms is coordinated to a Co^{III} center, electron transfer can take place far more rapidly than in *(4)* or *(5)*.

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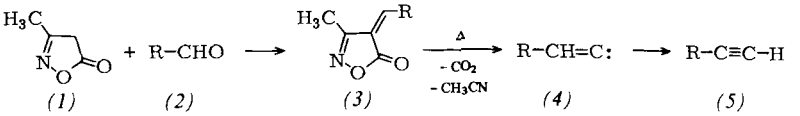
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[4] At 22 °C $k_{(4)} = (4.0 \pm 0.6) \times 10^8$ l/mol·s and $k_{(5)} = (4.2 \pm 0.4) \times 10^8$ l/mol·s. Free pyrazinecarboxylic acid reacts with formation of a stable radical ($k \approx 8.5 \times 10^8$ l/mol·s).
[5] For *(4)* at 22 °C: $k_p = 92 \pm 9\,s^{-1}$ and $k_d = 2.0 \pm 1.0\,s^{-1}$, and for *(5)*: 900 ± 90 and $18 \pm 4\,s^{-1}$ respectively.
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A General and Facile Synthesis of Aryl- and Heteroarylacetylenes[**]

By *Curt Wentrup* and *Hans-Wilhelm Winter*[*]

Flash pyrolysis is a useful experimental technique for the preparation of kinetically unstable, but thermodynamically stable compounds[1]. In a previous paper[2] we described the preparation of some simple arylacetylenes by flash pyrolysis of 4-arylmethylene-5(4*H*)-isoxazolones. We now report that this reaction permits the synthesis of several acetylenes whose preparation by classical methods is difficult or impossible.

Compounds *(3)* are generally obtained by condensation at room temperature of the corresponding aldehydes *(2)* with 3-methyl-5(4*H*)-isoxazolone *(1)* or its morpholine salt[3] in $CHCl_3$, ethanol, or mixtures of these solvents, or, in the case of *(3f)* and *(3h)* by refluxing in toluene/dimethylformamide[4] (Table 1).



(1) *(2)* *(3)* *(4)* *(5)*

Table 1. 4-Methylene-5(4*H*)-isoxazolones *(3)* and acetylenes *(5)*.

R = *(a)* *(b)* *(c)* *(d)* *(e)* *(f)* *(g)* *(h)*

Compd.	Yield [%] [a]	*(3)* M.p. [°C]	Pyrolysis temp. [°C] [b]	Yield [%]	*(5)* M.p. [°C] B.p. [°C/torr]	$\nu_{C\equiv C}$ [cm^{-1}]	ν_{CC-H}	Ref.
(a)	95	187—188	800	97	$40/10^{-2}$	2110	3325	
(b)	84 [c]	209—210	750	83	147—148/760	2110	3325	
(c)	69	145—146	800	95	131—132/760	2115	3310	[6]
(d)	40	140—141	800	65	134—135/760	2120	3315	[7]
(e)	74	151—153	800	80	126—127/760	2115	3310	
(f)	90	246—248	750	79	102 (dec.)	2105	3260	[8]
(g)	78	241—242	750	83	119	2108 [d]	3230	
(h)	70	218—219	700	93	35	2090	3285	

[a] Based on aldehydes *(2)*. [b] Pressure: 10^{-3}—10^{-4} torr. [c] Prepared by *W. Reichen*, Université de Lausanne. [d] Raman spectrum (IR inactive).

Flash pyrolysis of *(3a)*—*(3h)* at temperatures of 700—800 °C gave good yields of acetylenes *(5a)*—*(5h)*, presumably

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via the carbenes *(4)* (Table 1[4]). The pyrolysis temperatures reported are those giving the highest yields while avoiding the formation of tarry by-products. The acetylenes all tend to polymerize, but are easily purified by distillation or sublimation *in vacuo*. A case in point is 2-ethynylpyrrole *(5a)*, which rapidly polymerizes at room temperature, so that its preparation in solution by conventional methods would be highly problematical. Indeed, previous attempts to isolate this compound failed[5]. Nevertheless, *(5a)* is a thermodynamically very stable compound, surviving gas-phase pyrolysis at temperatures up to 1000°C, and isolable in near-quantitative yield on the pyrolysis of *(3a)* (Table 1).

The preparation of 3-ethynylindole *(5f)* in 20% yield by classical methods was recently described[8]. The yield obtained by the present method (79%) is superior.

The feasibility of flash pyrolysis as a preparative method depends, of course, on the volatility of the starting material. The isoxazolones *(3a)*—*(3h)* all sublime without difficulty at 120—180°C. However, in other cases, *e.g.* the preparation of *p*-nitrophenylacetylene from the corresponding isoxazolone derivative, only low yields were obtained due to extensive decomposition prior to volatilization of the starting material. In such cases we have found that good yields can be obtained by allowing the solid starting material to drop into a vertical pyrolysis tube.

Experimental

Synthesis of *(3a)*: A mixture of *(1)* (2.48 g, 0.025 mol) and pyrrole-2-carbaldehyde *(2a)* (2.38 g, 0.025 mol) in $CHCl_3$-EtOH (1:3) (80 ml) was stirred under N_2 at 22°C for 16 h. After concentrating to half volume, the brown-yellow crystals were filtered and recrystallized several times from $CHCl_3$-hexane, yielding 4.20 g (95%) of *(3a)* as yellow crystals of m.p. 187—188°C.

Synthesis of *(3h)*: To a solution of the morpholine salt[3] (0.93 g, 0.005 mol) of *(1)* in EtOH (20 ml) was added azulene-1-carbaldehyde *(2h)*[9] (0.78 g, 0.005 mol) in EtOH (20 ml), and the mixture was stirred at 22°C under N_2 for 24 h. Work-up as above and recrystallization from $CHCl_3$ (200 ml) furnished *(3h)* (0.83 g, 70%) as dark-red crystals of m.p. 218—219°C.

Synthesis of *(5a)*: A pyrolysis apparatus similar to that previously described[10] was used. At a pressure of *ca.* 10^{-3} torr and an oven temperature of 800°C, *(3a)* (0.4 g, 2.27 mmol) was sublimed from a flask maintained at 120°C in the course of 5 h. The products were collected on a cold-finger at −196°C. Acetonitrile and CO_2 were removed *in vacuo* by allowing the temperature to rise to *ca.* 20°C. *(5a)* (0.20 g; 97%) was isolated by vacuum transfer at 40°C (*ca.* 10^{-2} torr) into a receiver cooled in liq. N_2. ^{1}H-NMR (CCl_4): $\delta = 3.07$ (s, 1H), 6.07 (m, 1H), 6.41 (m, 1H), 6.62 (m, 1H), 8.2 (br., NH).

Synthesis of *(5h)*: In a manner similar to *(5a)*, *(5h)* was prepared in 93% yield as blue crystals of m.p. 35°C by pyrolysis of *(3h)* at 700°C, followed by sublimation of the product at 20°C/10^{-3} torr. ^{1}H-NMR (CCl_4): $\delta = 3.42$ (s, C≡C—H), 7.06—7.70 (m, 4H), 7.96 (d, H^2, $J_{23} = 4$ Hz), 8.26 (d, H^8, $J_{78} = 10$ Hz), 8.57 (d, H^4, $J_{45} = 10$ Hz).

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CAS Registry numbers:
(1), 1517-96-0; *(2a)*, 1003-29-8; *(2b)*, 1192-58-1; *(2c)*, 98-03-3; *(2d)*, 498-62-4; *(2e)*, 620-02-0; *(2f)*, 487-89-8; *(2g)*, 17422-74-1; *(2h)*, 7206-61-3; *(3a)*, 67237-43-8; *(3b)*, 67237-44-9; *(3c)*, 67237-45-0; *(3d)*, 67237-46-1; *(3e)*, 67237-47-2; *(3f)*, 67237-48-3; *(3g)*, 67237-49-4; *(3h)*, 67237-50-7; *(5a)*, 67237-51-8; *(5b)*, 67237-52-9; *(5c)*, 4298-52-6; *(5d)*, 67237-53-0; *(5e)*, 67237-54-1; *(5f)*, 62365-78-0; *(5g)*, 67271-48-1; *(5h)*, 67237-55-2

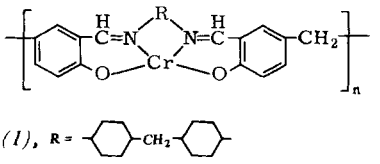
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Molecular Sieve Properties of Polymeric Schiff Base-Metal Complexes

By *Manfred Riederer* and *Wolfgang Sawodny*[*]

Materials exhibiting specific absorption features due to pore openings of molecular dimensions, and thus capable of physically separating molecules or atoms according to their size and shape, are called molecular sieves. Examples of such materials already well documented include the zeolites, activated charcoals, porous polymers, and porous glasses.

We recently reported the synthesis of novel polymeric Schiff-base complexes and their ability to form addition compounds with neutral molecules[1]. In the meantime we have also been able to demonstrate their selective adsorption capacity as a function of the critical diameter of the guest component. Data for the most effective of the compounds known so far, *i.e. (1)*, are listed in Table 1.



(1), R =

Table 1. Comparison of the adsorption capacities of compound *(1)*, zeolite and active charcoal molecular sieves in wt.-% (20°C, *ca.* 760 torr).

Adsorbate	Critical diameter [Å]	Adsorbant *(1)*	Zeolite [a]	Active charcoal [a]
Pyridine	5.24	65.75		
CCl_4	6.88	56.72		
Benzene	5.24	50.64	18.80	37.13
CH_3OH	3.00	34.03	10.90	
CH_2Cl_2	4.48	32.01		
Cumene	5.34	29.92		
Cyclohexane	5.37	26.92	19.60	21.00
n-Pentane	4.89	17.38	12.40	
H_2O	2.60	10.75	33.00	28.00
1,3,5-Triethylbenzene	9.00	0.00		

[a] Highest value from the literature.

With exception of the results for water, *(1)* shows a greater adsorption capacity than molecular sieves of the zeolite or active-charcoal type.

We have also investigated the behavior of the polymeric compound *(1)* when used as stationary phase in molecular

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sieve gas chromatography[2]. As an example of the efficiency of *(1)* as a molecular sieve, the complete separation of a mixture of noble gases (He, Ne, Ar, K, and Xe) except for He and Ne at room temperature is reproduced in Figure 1. Many other gases, such as Ar and O_2, can also be separated from each other in a similar way at room temperature.

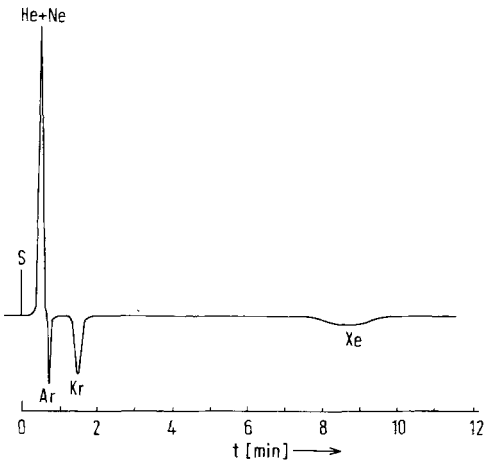


Fig. 1. GC separation of a noble gas mixture on *(1)* at 28 °C (column 200 × 0.2 cm, flow rate 30 ml/min, N_2).

Both the selective adsorption capacity of the polymeric Schiff-base complex *(1)* as well as its efficiency at separating gases in gas-chromatography are similar to that observed for zeolites of the type 13X having pore diameters of 8Å[3]. This lends support to the following molecular model (Fig. 2), based on the bond lengths and angles observed in the structure of Cu(salen)[4].

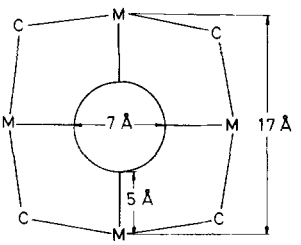


Fig. 2. Cavity in a possible helix structure of compound *(1)* (schematic).

Only the metal ion displaced from the ligand plane and the tetrahedral methylene carbon of the ligand bridge were considered, and were arranged assuming a helical structure. Such a polymeric molecule contains an internal cavity (diameter ≈ 7 Å), which is consistent with its selective adsorption capacity. Thus tetrachloromethane, with a diameter 6.88 Å, is quite readily adsorbed, whereas 1,3,5-triethylbenzene, with a diameter of 9 Å is not.

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CAS Registry number:
(1), 64440-58-0

[1] *W. Sawodny, M. Riederer*, Angew. Chem. *89*, 897 (1977); Angew. Chem. Int. Ed. Engl. *16*, 859 (1977); *M. Riederer, E. Urban, W. Sawodny, ibid. 89*, 898 (1977) and *16*, 860 (1977), respectively; *W. Sawodny, M. Riederer, E. Urban*, Inorg. Chim. Acta 29, 63 (1978).

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[4] *D. Hall, T. N. Waters*, J. Chem. Soc. *1960*, 2644.

Ring Contraction by Peracid Oxidation: Preparation of *cyclo*-Heptasulfur Dioxide, S_7O_2, from S_8[1]

By *Ralf Steudel* and *Torsten Sandow*[*]

Sulfur rings S_n (n = 6—8) are oxidized by trifluoroperacetic acid to the monoxides S_nO, which are isolable in pure form[2]. Only on reaction of the sulfanes R_2S_n (R = organyl, n = 3, 4) with an excess of peroxy acid have disulfoxides been obtained. However, they very readily decompose to sulfones, particularly if the sulfoxide groups are separated by only one sulfur atom[3].

In an attempt to oxidize S_8 with excess peroxy acid to S_8O_2, we found that S_7O_2 was formed and could be isolated in pure form in 5—10 % yield:

$$S_8 + 4CF_3CO_3H \rightarrow S_7O_2 + SO_2 + 4CF_3CO_2H$$

Even on extensive variation of the molecular ratio of the reactants there was no indication of a higher oxide of S_8; on the other hand, the reaction product sometimes contained traces of S_7O, which could be identified along with S_7O_2 by Raman spectroscopy. S_7O_2 could also be obtained from S_8O, S_7, and S_7O, but the yields were lower or at best the same.

The formation of S_7O_2 from S_8 most likely proceeds *via* the following steps:

$$S_8 \xrightarrow{+O} S_8O \xrightarrow{+O} [S_8O_2] \xrightarrow{+O} [S_8O_3] \xrightarrow{-SO_2} S_7O \xrightarrow{+O} S_7O_2$$

We assume that the hypothetical S_8O_2 is oxidized very much more rapidly than S_8O, so fast that it cannot be isolated, and that S_8O_3 immediately decomposes into S_7O and SO_2, since it must contain two SO groups which at most can be separated by only one sulfur atom. Decomposition of S_8O_2 into SO_2 and S_7 can be ruled out since S_7 has never been observed as an intermediate.

S_7O_2 forms dark-orange crystals, which are more intensely colored and much less stable than S_7O. At 60—62 °C spontaneous decomposition occurs with vigorous evolution of SO_2 and formation of polymeric sulfur. At 25 °C decomposition begins within a few minutes and is complete after 2 h in the dark. Heating in a vacuum (50—60 °C) leads to the characteristic decomposition product of polysulfur oxides, namely S_2O, which is also observed in the mass spectrum[4] besides SO^+ and S_n^+ (n = 1—8). The composition of S_7O_2 was determined by elemental analysis and osmometric determination of the relative molecular mass in CS_2.

S_7O_2 is far less soluble in CS_2 (*ca.* 1 g/l CS_2 at 0 °C) than S_7O; the solution decomposes within 1 h to S_6, S_7, S_8, and SO_2. The IR spectrum of a freshly prepared solution shows two strong absorptions at 1138 and 1127 cm^{-1}, which can be assigned to the two SO stretching vibrations.

The Raman spectrum[4] shows the typical lines of the S_7 ring in the region 150—280 cm^{-1}, as well as the SO— stretching and SSO deformation vibrations characteristic for the —S—SO—S— groups (Table 1). Assignment of the signals is based on a comparison with the spectra of S_7[5] and S_7O[6]. There is a distinct connection between the wave numbers of the SS stretching vibrations of sulfur rings and the lengths of the corresponding bonds[7] from which the values for the

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SS bond distances in S_7O_2 can be derived using the wave numbers given in Table 1. On the basis of these values, and observations made in structural studies on S_8O[8a] and S_7O[8b], we suggest the following structure for S_7O_2 (bond lengths in pm):

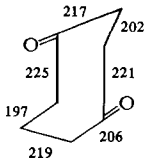


Table 1. Normal modes of solid S_7O_2 (cm^{-1}; Raman intensities in parentheses).

	Assignment		Assignment
1117(4)	ν_{SO}	333(100)	ν_{SS}
1103(16)		300(55)	
1083(23)		277(70)	δ_{ring}
559(10)	ν_{SS}	262(5)	
505(31)		240(36)	
461(14)		230(47)	
407(38)	δ_{SSO}	186(52)	
402(44)		178(13)	
384(24)		160(59)	τ_{ring}
378(41)		151(50)	
356(63)	ν_{SS}		
344(26)			

In this isomer the SO groups, generally observed in an axial array, are at the maximum possible distance.

Procedure

To a solution of S_8 (2.8 g) in analytically pure CH_2Cl_2 (800 ml) is added dropwise 139 ml CF_3CO_3H solution[2] (0.39 mmol CF_3CO_3H/ml; molar ratio S_8: $CF_3CO_3H = 1:5$) at −20 °C. After 2 hours' stirring the reaction mixture is cooled to −78 °C and the colorless CF_3CO_2H that crystallizes out is separated off on a coolable glass frit (−30 °C). The filtrate is treated with 500 ml *n*-hexane at −20 °C, and then allowed to stand for 14 days at −50 °C. The orange-red, crystalline crude product (1.2—1.6 g) is filtered off at −30 °C, dissolved in 1 l anhydrous CS_2 at 0 °C, filtered, and cooled to −78 °C. 100—300 mg S_7O_2 (4—11 %) crystallizes out.

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CAS Registry numbers:
S_8, 10544-50-0; CF_3CO_3H, 359-48-8; S_7O_2, 67238-13-5

[1] Part 57 on Sulfur Compounds.—Part 56: *R. Steudel, H.-J. Mäusle*, Z. Naturforsch. *A*, in press.
[2] *R. Steudel, J. Steidel*, Angew. Chem. *90*, 134 (1978); Angew. Chem. Int. Ed. Engl. *17*, 134 (1978) and references cited therein.
[3] *R. Steudel, J. Latte*, Chem. Ber. *110*, 423 (1977).
[4] Varian MAT 311 A mass spectrometer, FDIFJ source (70 eV), sample temperature 12 °C; Cary 82 Raman spectrometer, krypton laser 647.1 nm, sample temperature −100 °C.
[5] *R. Steudel, F. Schuster*, J. Mol. Struct. *44*, 143 (1978).
[6] *R. Steudel, T. Sandow*, Angew. Chem. *88*, 854 (1976); Angew. Chem. Int. Ed. Engl. *15*, 772 (1976), and unpublished results.
[7] *R. Steudel*, Z. Naturforsch. *B 30*, 281 (1975); the spectra and structures of S_7, S_8, S_{12}, S_7O, S_8O, BaS_3, Na_2S_4 and $(NH_4)_2S_5$ give for cumulated SS bonds the relationship $\log d = 2.881 - 0.213 \times \log \nu$ (d in pm, ν in cm^{-1}; correlation coefficient 0.99).
[8] a) *P. Luger, H. Bradaczek, R. Steudel, M. Rebsch*, Chem. Ber. *109*, 180 (1976); b) *R. Steudel, R. Reinhardt, T. Sandow*, Angew. Chem. *89*, 757 (1977); Angew. Chem. Int. Ed. Engl. *16*, 716 (1977).

Complete Enantiomer Separation by Chromatography on Potato Starch

By *Heinrich Hess, Günther Burger*, and *Hans Musso*[*]

The enantiomers of numerous chiral biphenyl compounds[1,2] and amino acid derivatives[3] can be enriched in the front and end fractions by chromatography on potato starch. In some cases they have even been isolated optically pure in small amounts.

It has now been found that, in many cases, by proper choice of buffer salt, its concentration and pH value, and temperature, complete separation of enantiomers can be achieved on 130 cm columns which, as shown for example by *(1)* and *(4a)*, can frequently be of preparative use. The UV spectroscopically and polarimetrically measured elution diagrams shown in Figures 1—3 illustrate some of these separations. Figure 1 indicates how the efficiency of separation

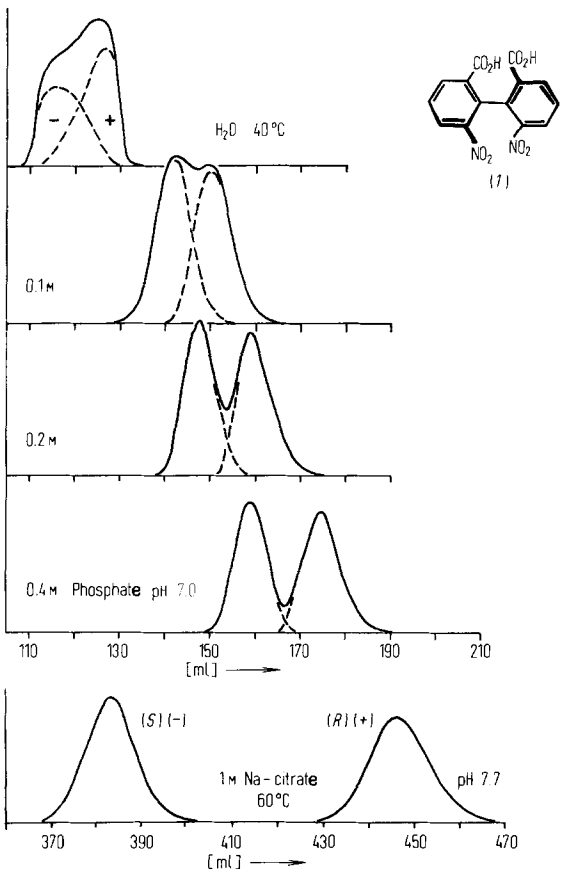


Fig. 1. Elution diagram for 2 mg each of (+)- and (−)-6,6'-dinitrodiphenic acid *(1)* on a 1.6 cm × 135 cm column.

increases with increasing buffer concentration in the case of 6,6'-dinitrodiphenic acid *(1)*. In the case of the *m*-linked trimers of orcinol *(3)* there is a DL form and a *meso* form. Chromatographic separation on potato starch enabled assignment of the two different structures (Fig. 2)[1c]. All three diastereomeric racemates *(4a)*—*(4c)* of the homologous tetramer *(4)*[1] can be cleanly separated (Fig. 3)[4]. Preparative separation of *(4a)* is especially simple: the (−)-enantiomer is washed through a relatively short column with water; the (+)-form is almost completely retained on the column and can be

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eluted with increasing concentration of methanol. As a rule, increasing temperature reduces tailing and improves the separation. In the case of 2,4,2',4'-tetrahydroxy-6,6'-dimethylbiphenyl *(2)*, a reversal of selectivity is observed with incomplete separation: at 20 °C the (*R*)-(+)-enantiomer is first eluted[1b], at 59 °C the (*S*)-(−)-enantiomer[5].

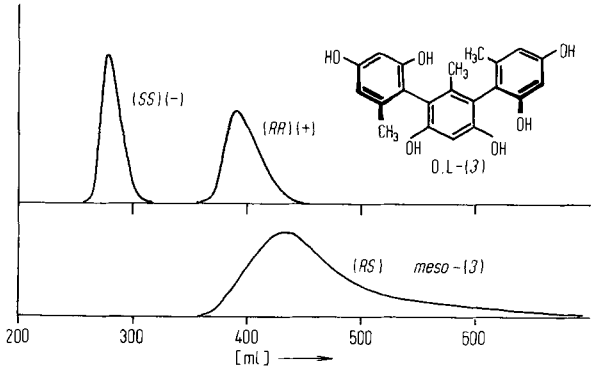
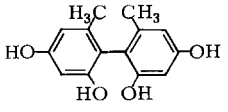
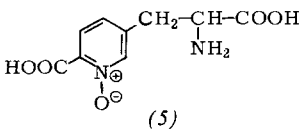


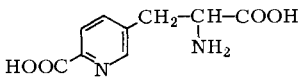
Fig. 2. Elution diagram for 50 mg each of *rac*- and *meso*-trimeric *(3)* on a 2 cm × 130 cm column; 0.2 M phosphate buffer, pH = 7. Rotation values and yields of the pure enantiomers, see [1c].



(2)



(5)



(6)

The precursors required for a biogenic-like synthesis of muscaflavin[6], the *rac.* carboxypyridylalanine derivatives *(5)* and *(6)*[7], have been analytically resolved on the first run on the starch column; the preparative separation meets with difficulties owing to the low column capacity and the large amounts of buffer salt.

Two preparative procedures for the isolation of optically pure enantiomers of *(1)* and *(4a)* demonstrate that it is worthwhile searching for the right conditions for complete separation of enantiomers on cheap natural products such as potato starch.

Procedures

Separation of enantiomers of 6,6'-dinitrodiphenic acid *(1)*: A warm solution of 500 mg of *(1)* and 120 mg of sodium hydroxide in 5 ml of 1.5 M sodium citrate buffer (pH = 7.9) was transferred to a 5.2 cm × 136 cm column and eluted at 80 °C with the same buffer (70 ml/h). The fractions from 5.60—6.61 l contained the pure (*S*)-(−) enantiomer, that from 6.74—7.85 l the pure (*R*)-(+) enantiomer. The intermediate fractions contained 1.2 % of the starting materials. The (*S*)-(−) and (*R*)-(+) fractions were each acidified with 150 g phosphoric acid/l eluate to pH = 4 and extracted with ethyl acetate. Recrystallization from water afforded: 190 mg (*S*)-(−)-*(1)*, m.p. 230—233 °C, $[\alpha]_D^{20} = -137.6°$; 190 mg (*R*)-(+)-*(1)*, m.p. 230—233 °C, $[\alpha]_D^{20} = +138°$ (*c* = 1, ethanol)[8, 9].

Separation of (*S*,*S*,*S*)-(−)- and (*R*,*R*,*R*)-(+)-2,4,2',4',2'',4'',2''',4'''-octahydroxy-6,6',6'',6'''-tetramethyl-*m*,*m*-quaterphenyl *(4a)*: A solution of 200 mg *(4a)* in 40 ml hot water was transferred to a 5.5 cm × 34 cm column and eluted at room temperature with water (3 fractions at 13 ml/h). The fractions 630—1080 ml contained the pure (−)-enantiomer. From 900 ml onwards the eluant solvent was continuously mixed with methanol in the 600 ml supply flask. The fractions 1700—2200 ml (70 % CH_3OH) contained the (+)-enantiomer. The residues obtained from both fractions by evaporation had to be purified on SiO_2 thin-layer plates with ethyl acetate/chloroform (7:3) for separation from dissolved starch. The recovered zones were eluted with acetone and the residues

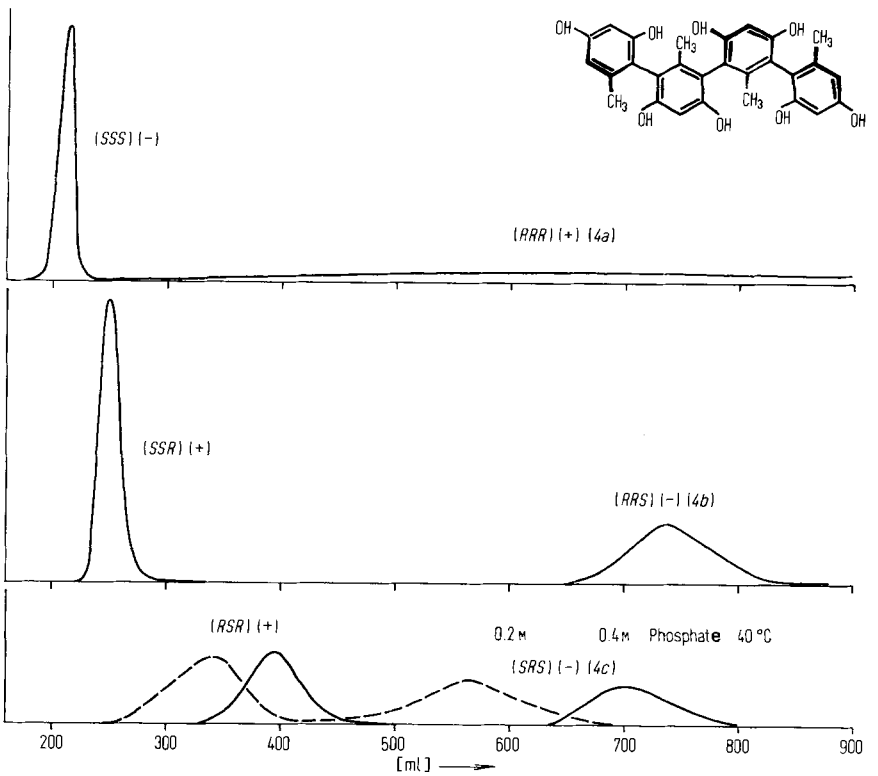


Fig. 3. Separation of diastereomeric *rac*-tetrameric *(4a)*—*(4c)*, 2 mg each, 1.6 cm × 134 cm column; 0.2 M phosphate buffer, pH = 7.

obtained after removal of solvent were recrystallized from ether/chloroform at 0 °C.

(S,S,S)-(−)-*(4a)*: 80 mg of almost colorless needle clusters, m.p. 227—279 °C, $[\alpha]_D^{20} = -6.8°$ ($c = 3.5$, ethanol); *(R,R,R)*-(+)-*(4a)*: 60 mg (colored pink by autoxidation), m.p. 240—276 °C, $[\alpha]_D^{20} = +6.5°$ ($c = 3.5$)[9].

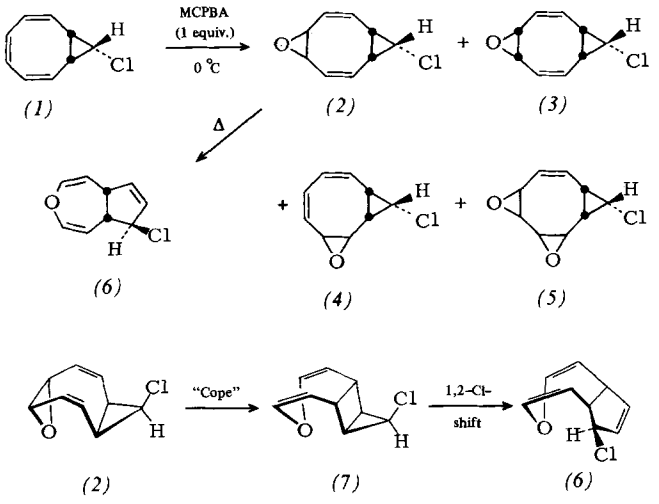
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[1] a) *H. Musso*, Chem. Ber. *91*, 349 (1958); b) *W. Steckelberg, M. Bloch, H. Musso, ibid. 101*, 1510, 1519 (1968); c) *R. K. Haynes, H. Hess, H. Musso, ibid. 107*, 3733 (1974).
[2] *H. Krebs, H. Schumacher*, Chem. Ber. *99*, 1341 (1966).
[3] *H. Krebs, J. A. Wagner, J. Diewald*, Chem. Ber. *89*, 1875 (1956); *W. Lautsch, D. Heinicke*, Kolloid-Z. *154*, 1 (1957).
[4] The absolute configuration of *(2)*—*(4)* was deduced by chemical correlation from *(1)*[1b, 5].
[5] *H. Hess*, Dissertation, Universität Karlsruhe 1978.
[6] *R. v. Ardenne, H. Döpp, H. Musso, W. Steglich*, Z. Naturforsch. *C 29*, 637 (1974).
[7] *H. Barth*, Dissertation, Universität Karlsruhe 1976.
[8] Literature m.p. 231—233 °C: *E. Späth, F. Kesztler*, Ber. Dtsch. Chem. Ges. *69*, 2725 (1936); $[\alpha]_D^{27} = +133.7°$ ($c = 2$, ethanol); *A. W. Ingersoll, J. R. Little*, J. Am. Chem. Soc. *56*, 2123 (1934) [9].
[9] The $[\alpha]_D$ values of *(1)* and *(4a)* decrease markedly with increasing concentration and temperature; under identical conditions, very good agreement is obtained.

Conformationally Induced Stereospecificity in the Multiple Epoxidation of *syn*-9-Chloro-*cis*-bicyclo-[6.1.0]nona-2,4,6-triene[**]

By *A. G. Anastassiou* and *R. L. Mahaffey*[*]

In work associated with our quest for novel nonbenzenoid aromatics[1] and specifically directed at the synthesis and study of monohetero and polyhetero annulenyl ions, we prepared a number of multicyclic progenitors *via* selective epoxidation of one or more of the π units of *syn*-9-chloro-*cis*-bicyclo[6.1.0]nona-2,4,6-triene *(1)*, *i.e.* a molecule whose "bridge" substituent is potentially capable of anionically or cationically assisted extrusion. Our specific choice of the sterically constrained extended *syn* epimer over the more flexible *anti* variant stemmed from an attempt to minimize the formation of undesirable stereoisomeric mixtures in the various steps.



Scheme 1.

Prolonged (5 days) exposure of *(1)* to an equivalent quantity of *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 at *ca.* 0 °C led, in 84 % yield (78 % conversion), to a four-component mixture consisting[2] of two symmetrical (^{1}H-NMR) monoepoxides, *(2)* (50 %) (m.p. 71—72 °C)[3] and *(3)* (20 %) (m.p. 92.5—93.5 °C)[3], one unsymmetrical monoepoxide *(4)* (8 %) (liquid)[3] and one unsymmetrical diepoxide *(5)* (22 %) (m.p. 87.5—88.5 °C)[3]. The specific stereochemical assignments depicted in *(2)* and *(3)* were made on the basis of ^{1}H-NMR shift studies (Fig. 1). Chemically, these assignments were secure-

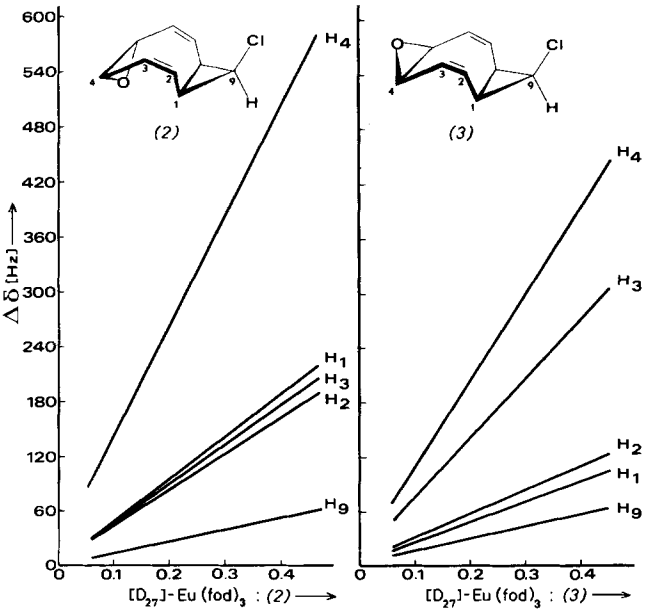


Fig. 1. Plot of *downfield* ^{1}H-NMR chemical shift Δδ *vs.* molar ratio of $[D_{27}]$Eu(fod)$_3$:*trans*-monoepoxide *(2)* (left) and $[D_{27}]$Eu(fod)$_3$:*cis*-monoepoxide *(3)* (right).

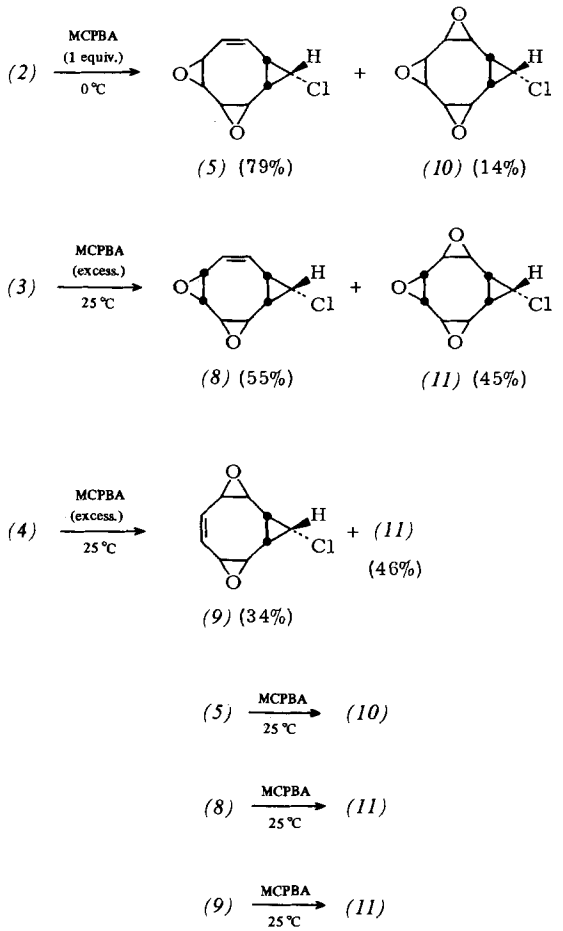
ly validated through the ability of the *trans* isomer *(2)* to undergo ready, clean, rearrangement to *(6)* upon heating at 100 °C ($\Delta G^{\ddagger} = 28.5$ kcal/mol)[4] and the complete resistance of the *cis* counterpart *(3)* to undergo any type of bond relocation on prolonged heating at 140 °C. The rationale behind this "chemical" distinction between *(2)* and *(3)* is, of course, that of the two substances only the former *(trans)* may, and in fact must for steric reasons, incorporate an oxirane function which is "folded" with respect to the eight-membered nucleus and thus properly directed to undergo "Cope" rearrangement[5] to *(7)* (unobserved)[6] which must obviously act as intermediate in the formation of *(6)*[7] (Scheme 1).

Additional exposure of *(2)*, *(3)*, and *(4)* to MCPBA at ambient temperature led to the formation of the various di- and trioxiranes depicted in Scheme 2. The structures of these substances, which obviously are properly constituted for potentially direct conversion to the desired dioxa- and trioxa-annulenyl ions, were established through fully consistent spectroscopic data.

With regard to mechanism it is perhaps interesting to note that the formation of dioxiranes *(5)*, *(8)*, and *(9)* from their respective monofunctional variants *(2)*, *(3)*, and *(4)* invariably occurs stereospecifically, *via exo* delivery of the oxygen function. Further, brief inspection of trioxiranes *(10)* and *(11)* reveals that their formation from the corresponding dioxiranes is similarly controlled. One significant point to

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Scheme 2.

note in this connection is, of course, that *exo* addition *per se* does not fulfill the requirement for stereospecific generation of product and that it is only expected to do so when applied to a reactant which is rigidly held in a specific nonplanar arrangement such as the "extended" form adopted by *(1)*. Basically then, what one has here is a situation where product stereospecificity is realized strictly under the influence of conformational control[8].

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CAS Registry numbers:
(1), 698-96-4; *(2)*, 67271-42-5; *(3)*, 67335-55-1; *(4)*, 67271-43-6; *(5)*, 67271-44-7; *(6)*, 67271-45-8; *(8)*, 67335-56-2; *(9)*, 67271-46-9; *(10)*, 67271-47-0; *(11)*, 67335-57-3

[1] For a review on the subject see: *A. G. Anastassiou*, Pure Appl. Chem. *44*, 691 (1975).

[2] The mixture was separated into its individual components by column chromatography (Al_2O_3) at *ca.* −15 °C. Subsequent purification entailed distillation for the liquids and recrystallization for the solids.

[3] Confirmed by ^{1}H-NMR, UV, IR, and MS.

[4] Calculated from the rate of consumption of *(2)* as monitored by ^{1}H-NMR spectroscopy.

[5] The requirement for a "folded" geometry in the "Cope" rearrangement of a *cis*-bicyclo[6.1.0]nona-2,4,6-triene was recognized several years ago; *A. G. Anastassiou, R. C. Griffith*, J. Am. Chem. Soc. *93*, 3083 (1971).

[6] For a related case where the dioxa analog of *(2)* thermolyzes to a tricyclic molecule analogous to *(7)* see: *A. G. Anastassiou, E. Reichmanis*, J. Org. Chem., in press.

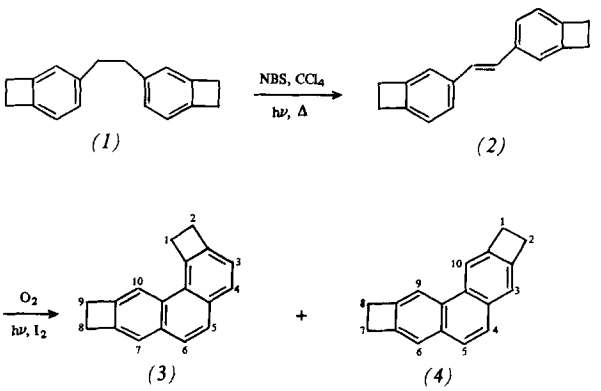
[7] It is pertinent to note in this context that the *syn* disposition of the chlorine atom in *(7)* renders it readily amenable to cyclopropane-assisted 1,2-migration. For a detailed description of this phenomenon see: *R. B. Woodward, R. Hoffmann:* The Conservation of Orbital Symmetry. Verlag Chemie, Weinheim/Academic Press, New York 1970, Ch. 5, pp. 46—48.

[8] It is noteworthy that *exo* epoxidation of the hypothetical conformers of the various mono- and diepoxides described here, *i. e.*, those incorporating a folded cyclopropane appendage should produce stereoisomers of the di- and triepoxides observed in this work.

1,2,8,9-Tetrahydrodicyclobuta[*b*,*g*]phenanthrene and 1,2,7,8-Tetrahydrodicyclobuta[*b*,*h*]phenanthrene, Potentially Carcinogenic Activated Hydrocarbons[**]

By *P. Perkins* and *K. P. C. Vollhardt*[*]

Polycyclic aromatic hydrocarbons have become the subject of renewed vigorous research activity in connection with carcinogenesis by environmental pollutants[1] and the mechanism of hydrogenation of coal[2]. We have embarked on a program aimed at studying the effect of multiple strained ring activation[3] on the physical and chemical properties of polycyclic benzenoids. We now report the synthesis of the title compounds *(3)* and *(4)*, the first isomeric and doubly activated members in the series. Moreover, compound *(3)* is the first example of mutagenicity due to strained ring activation of a benzenoid hydrocarbon.



Cobalt-catalyzed trimerization[4] of 1,5-hexadiyne (*n*-octane, 126 °C, high dilution) gave *(1)*[5] in 55% yield. Photolytic NBS-bromination (boiling CCl_4) furnished the *trans*-stilbene *(2)* as colorless, slightly air-sensitive crystals[6, 7]. Iodine-catalyzed oxidative photocyclization[8] of *(2)* resulted in the desired activated phenanthrenes *(3)* and *(4)* (ratio 2:1) which could be separated by gas chromatography (0.7 × 168 cm Al column, 5% SE-30 on 60/80 Chrom-W-Aw, 220 °C) as colorless air- and heat-sensitive crystals[6, 7]. The electronic spectra of *(3)* and *(4)* in comparison with the parent phenanthrene system reveal the consequences of strained ring fusion in progressively bathochromic shifts and increased extinction coefficients (Fig. 1). The "bay-region" isomer *(3)* shows a particularly pronounced effect. This compound also exhibits an unusually shielded ($\delta = 7.88$) "bay-region" proton H^{10} in the ^{1}H-NMR spectrum[7] compared with H^4 in phenanthrene ($\delta = 8.62$), or the calculated value for H^4 in 2,3,5,6-tetramethyl-

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phenanthrene ($\delta = 8.47$)[9]. This probably reflects removal of the deshielding steric effect of the opposite bay proton (in phenanthrene) and tying of the methylene substituent back into the small ring. The difference between the calculated and observed value ($\Delta\delta = 0.59$ ppm) could be a measure of the true bay region steric effect in phenanthrene[10].

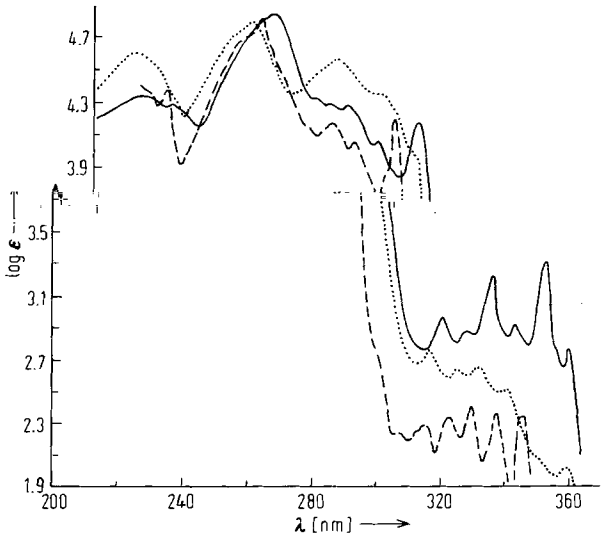
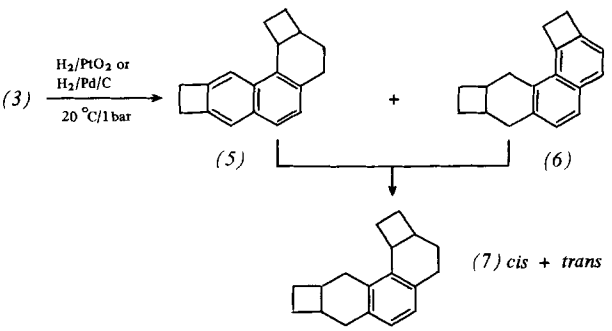


Fig. 1. Electronic spectra of *(3)* (——), *(4)* (···) and phenanthrene (– – –) in cyclohexane.

The consequences of strained ring activation are manifested in the chemical behavior of *(3)* and *(4)*. Thus, for example, rapid hydrogenation of *(3)* occurs under mild conditions exclusively at the outside rings and in a stepwise manner *via* the tetrahydro derivatives *(5)* and *(6)* (separable from *(3)* and *(7)* by charge transfer chromatography[11]) to eventually give *(7)* as an almost equal mixture of isomers[6]. This contrasts with the behavior of phenanthrene itself which is hydrogenated only under pressure and then only in the K region[12]. Interestingly, in competitive hydrogenations, we have also found *(3)* to be twice as reactive as *(4)*, as might be expected on the basis of bond-fixation arguments. The precursor *(1)* is hydrogenated only very slowly over PtO_2 or Pd/C (RT, 1 bar).



We have completed carefully standardized mutagenicity tests on the "bay region" isomer *(3)* (*Salmonella typhimurium*, "Ames test") and conclude that it has to be regarded as a weak mutagen. On the other hand *(4)* appeared inactive in this test. Phenanthrene was *inactive* and benzo[*a*]pyrene strongly active, as previously reported[13]. This constitutes the first indication that strained ring fusion at certain positions may transform a noncarcinogenic polycyclic hydrocarbon nucleus into a potential carcinogen. Caution should be exercised when working with activated compounds of this type.

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[1] *R. Freudenthal, P. W. Jones:* Carcinogenesis—A Comprehensive Survey. Vol. 1. Raven Press, New York 1976.
[2] *J. Falbe:* Chemierohstoffe aus Kohle. Thieme, Stuttgart 1977.
[3] *R. L. Funk, K. P. C. Vollhardt*, Angew. Chem. *88*, 61 (1976); Angew. Chem. Int. Ed. Engl. *15*, 53 (1976).
[4] *K. P. C. Vollhardt*, Acc. Chem. Res. *10*, 1 (1977).
[5] *A. J. Hubert, J. Dale*, J. Chem. Soc. *1965*, 3160.
[6] All new compounds isolated gave satisfactory analytical and/or spectral data.
[7] *(2)*, m.p. 126—127 °C (from ether); yield 72 %; ^{1}H-NMR (CCl_4, TMS): $\delta = 3.12$ (s, 8H), 6.81 (dd, $J = 7$, 1.5 Hz, 2H), 6.82 (s, 2H), 7.05 (br. s, 2H), 7.12 (dd, $J = 7$, 1.5 Hz, 2H); IR (KBr): 2924, 1473, 1203, 966, 877, 824 cm^{-1}; MS: $m/e = 232$ (M^+, 85 %), 202 (100 %); *(3)*, m.p. 120—130 °C dec. (from ether); yield 36 %; ^{1}H-NMR (CCl_4, TMS): $\delta = 3.25$ (m, 2H, H^2), 3.33 (s, 4H, $H^{8,9}$), 3.62 (m, 2H, H^1), 7.08 (br. d, $J = 8$ Hz, 1H, H^3), 7.32 (br. s, 1H, H^7), 7.45 (s, 2H, $H^{5,6}$), 7.55 (br. d, $J = 8$ Hz, 1H, H^4), 7.88 (br. s, 1H, H^{10}); IR (KBr): 2915, 874, 867, 844, 835 cm^{-1}; MS: $m/e = 230$ (M^+, 100 %), 229 (64 %); *(4)*, m.p. 120—130 °C dec. (from ether); yield 18 %; ^{1}H-NMR (CCl_4, TMS): $\delta = 3.34$ (s, 8H, $H^{1,2,7,8}$), 7.35 (s, 2H, $H^{3,6}$), 7.48 (s, 2H, $H^{4,5}$), 8.17 (s, 2H, $H^{9,10}$); IR (KBr): 2924, 883, 868 cm^{-1}; MS: $m/e = 230$ (M^+, 100 %), 202 (33 %).
[8] *F. B. Mallory, C. S. Wood, J. T. Gordon*, J. Am. Chem. Soc. *86*, 3094 (1964).
[9] This value was computed assuming additive effects of progressive methyl substitution on the phenanthrene nucleus: *K. D. Bartle, J. A. S. Smith*, Spectrochim. Acta *23 A*, 1689 (1967).
[10] See: *B. V. Cheney*, J. Am. Chem. Soc. *90*, 5386 (1968); *E. Ege, H. Vogler*, Tetrahedron *31*, 569 (1975); *M. Barfield, D. M. Grant, D. Ikenberry*, J. Am. Chem. Soc. 97, 6956 (1975); *H. P. Figeys, N. Defay, R. H. Martin, J. F. W. McOmie, B. E. Ayres, J. B. Chadwick*, Tetrahedron *32*, 2571 (1976).
[11] *R. G. Harvey, M. Halonen*, J. Chromatogr. *25*, 294 (1966).
[12] *P. P. Fu, R. G. Harvey*, Tetrahedron Lett. *1977*, 415.
[13] *J. McCann, E. Choi, E. Yamazaki, B. N. Ames*, Proc. Nat. Acad. Sci. USA *72*, 5135 (1975).

IR Spectroscopic Detection of Molecular SiO_2[**]

By *Hansgeorg Schnöckel*[*]

In recent years the matrix isolation technique has permitted the spectroscopic investigation of many compounds in monomeric form, which under normal conditions have highly cross-linked structures[1]. Particles evaporating from a Knudsen cell are quenched with a large excess of an inert gas on a cold surface. If evaporation of the monomer from a solid compound is not possible owing to decomposition reactions, attempts are made to synthesize them on the cold surface by cocondensation of reactive components. Thus, *Bos* and *Ogden*[2] have obtained monomeric GeO_2 and SnO_2 by cocondensation of the respective metal vapor and O_2 in a matrix and characterized them by vibrational spectroscopy. The matrix isolation of SiO_2, however, has to our knowledge not been reported so far.

Since a comparison of the molecules SiO_2 and CO_2 is of special interest we have attempted the matrix isolation of monomeric SiO_2 *via* a novel route. SiO evaporated from a Knudsen cell was cocondensed in argon as matrix substance with atomic oxygen generated by microwave excitation[3]. Parallel experiments were also carried out with ^{18}O- enriched SiO and O_2.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft. We thank *H. J. Göcke* for assistance with the experiments.

The IR matrix spectra show strong signals of O_3 and unreacted SiO together with moderately strong bands in the region of 1400 cm^{-1}, which are assigned to the ν_3-vibration of the SiO_2 molecule (see Fig. 1). In addition weaker satellite bands are observed at about 26 and 53 cm^{-1} lower wavelengths, which are ascribed to association of SiO_2 particles with O_2 molecules. Such effects have been established on a number of occasions in the matrix spectra of reactive particles in the presence of O_2 or N_2[4]. After correction for anharmonicity the measured $^{16}O/^{18}O$ shift of ν_3 is 37.1 cm^{-1}[5]; it agrees within the limits of accuracy with the shift of 37.2 cm^{-1} calculated for a linear SiO_2 molecule[6].

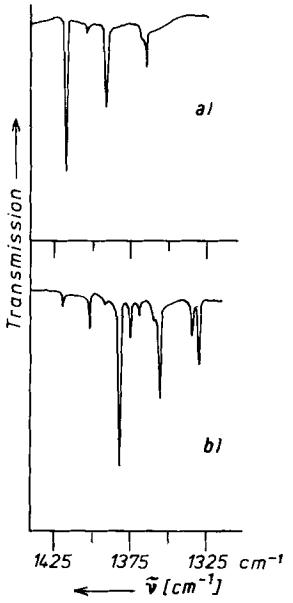


Fig. 1. Section of a IR-argon matrix spectrum after cocondensation of (a) $Si^{16}O + {}^{16}O$; (b) $Si^{18}O + {}^{18}O$.

From the observed value ν_3 one can immediately calculate the symmetry force constants $f_r - f_{rr} = 8.82 \times 10^2$ Nm^{-1} for monomeric SiO_2. The exact calculation of the valence force constant f_r is not possible without knowledge of ν_1. The determination of f_{rr} by additional evaluation of the isotopic shift $\Delta\nu_3$ in the case of $Si^{16}O^{18}O$ did not yield a meaningful result due to a limited accuracy of ± 0.15 cm^{-1} arising from anharmonicity and matrix effects. Hence, on the basis of data for comparison compounds (some siloxanes[7] and the isoelectronic AlFO investigated by us[8]) we estimate an expected value of 0.04 for the ratio f_{rr} to f_r in SiO_2. The valence force constant f_r of SiO_2 obtained using this value is given in Table 1 together with other valence force constants for CO and SiO bonds.

Table 1. Valence force constants f_r [10^2 Nm^{-1}] calculated from observed frequencies.

	Siebert rule [a]					
	>C—O—	>Si—O—	CO_2 [a]	SiO_2	CO [b]	SiO [b]
f_r	5.4	3.8	15.6	9.2	18.6	9.1

[a] *H. Siebert*: Anwendungen der Schwingungsspektroskopie in der anorganischen Chemie. Springer-Verlag, Berlin 1966.
[b] Cf. Ref. [5b].

The decrease $f(CO) \rightarrow f(SiO)$ in comparable compounds is not surprising, since as a rule the valence force constants for bonds between elements of the 1st period are considerably greater than for those in combinations of elements of the 2nd or of the 1st ad 2nd periods [$f(N_2) = 22.4$, $f(P_2) = 5.5 \times 10^2$ Nm^{-1}][5b].

According to the Siebert rule the bond order of the CO_2 molecule is 2.9, and that of the SiO_2 molecule is 2.5. This would indicate a considerable strengthening of the bonding in comparison with a double bond, which so far has not been satisfactorily explained even in the case of CO_2. In a similar way, bond orders of 2.0 and 1.9, respectively, have been calculated for the higher homologs GeO_2 and SnO_2[2]. A comparison of the force constants of SiO and SiO_2 shows that silicon itself can only link to oxygen *via* a double bond in the SiO molecule, whereas carbon in the CO molecule is coupled to the oxygen *via* a triple bond.

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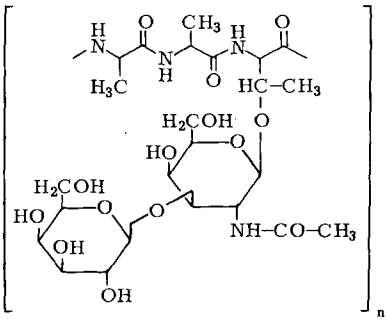
CAS Registry number:
SiO_2, 7631-86-9

[1] *A. Snelson* in *H. E. Hallam*: Vibrational Spectroscopy of Trapped Species. Wiley, New York 1973, pp. 203—244.
[2] *A. Bos, J. S. Ogden*, J. Phys. Chem. *77*, 1513 (1973); *A. Bos, J. S. Ogden, L. Orgee, ibid. 78*, 1763 (1974).
[3] Such matrix reactions with atomic oxygen have already enabled us to carry out the first isolation of monomeric AlFO and GaFO: *H. Schnöckel, H. J. Göcke*, J. Mol. Struct., in press.
[4] *D. A. van Leirsburg, C. W. DeKock*, J. Chem. Phys. *78*, 134 (1974); *H. Schnöckel*, Z. Anorg. Allg. Chem. *424*, 203 (1976); J. Mol. Struct., in press.
[5] a) *H. J. Becher*, Fortschr. Chem. Forsch. *10*, 156 (1968); b) *G. Herzberg*: Molecular Spectra and Molecular Structure, Vol. I. Spectra of Diatomic Molecules. Van Nostrand, New York 1950.
[6] The linearity of the monomeric SiO_2 molecule was also deduced from the deflection of molecular beams in electric fields: *M. Kaufman, J. Muenter, W. Klemperer*, J. Chem. Phys. *47*, 3365 (1967).
[7] *H. Bürger, U. Goetze, W. Sawodny*, Spectrochim. Acta *24 A*, 2003 (1968).
[8] *H. Schnöckel*, J. Mol. Struct., in press.

ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

The possibilities of reducing the freezing temperature in biological systems are considered by *Yin Yeh* and *R. E. Feeney*. Antarctic fish species were found to contain a group of very similar glycoproteins (AFGP) as natural antifreeze agents, while an Arctic fish contained just one major antifreeze protein of molecular weight ≈ 10000. Owing to the presence of AFGP and dialyzable salts, the serum of the Antarctic fishes freezes at -2.0°C whereas the freezing point of the seawater at the same location is -1.9°C. Experimental results obtained to date suggest that the antifreeze action is due primarily to



AFGP
n = 17-50

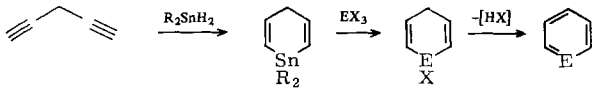
interactions with the surfaces of very small ice crystals, preventing further growth. [Anomalous Depression of the Freezing Temperature in a Biological System. Acc. Chem. Res. *11*, 129—135 (1978); 46 references]

[Rd 28 IE]

Solid electrolytes based on silver iodide are considered by *S. Geller*. The electrolytic conductivity in a true solid electrolyte is an inherent property of the crystal and is directly related to the crystal structure. Such a structure characteristically has (i) a large number of sites available to the mobile cations (or in some cases anions), (ii) a system of passageways resulting from the face-sharing of anion polyhedra (in some cases anion and cation polyhedra). The solid electrolyte with the highest conductivity is $RbAg_4I_5$; other remarkable compounds of this kind are $(C_5H_5NH)Ag_5I_6$, $(C_5H_5NH)_5Ag_{18}I_{23}$, and $Ag_{26}I_{28}W_4O_{16}$. [Silver Iodide Based Solid Electrolytes. Acc. Chem. Res. *11*, 87—94 (1978); 42 references]

[Rd 22 IE]

λ^3-Heterobenzenes containing Group V elements are the topic of a review by *A. J. Ashe, III*. In this context, particular interest attaches to the question whether the resemblance between the parent compound benzene *(1a)* and the first member of the hetero series pyridine *(1b)* extends to the other members of the series. *(1c)* through *(1f)* were synthesized from 1,4-pentadiyne. *(1c)* and *(1d)* are somewhat air-sensitive but distillable; *(1e)* can be isolated but polymerizes at room temperature; and *(1f)* can only be detected spectroscopically and *via* chemical trapping. The λ^3-heterobenzenes



(1)

(c), E = P; *(d)*, E = As; *(e)*, E = Sb; *(f)*, E = Bi

are shown by their spectra to be strongly aromatic. *(1c)* through *(1f)* were also found to resemble benzene in the cycloaddition of hexafluoro-2-butyne. [The Group 5 Heterobenzenes. Acc. Chem. Res. *11*, 153—157 (1978); 54 references]

[Rd 29 IE]

Affinity chromatography on columns containing nucleic acids is described in an article by *H. Potuzak* and *P. D. Degn*. The coupling of nucleic acids to a matrix, *e.g.* cellulose, can be achieved even by simple adsorption, but affinity adsorbents with higher capacity and stronger bonding between nucleic acid and matrix have to be prepared by chemical coupling. Chemical binding can be accomplished by UV-irradiation, by activation of the matrix with cyanogen bromide, or by reaction of matrix with ligand under the influence of carbodiimides or bisoxiranes. Affinity adsorbents containing nucleic acids are suitable for hybridizations with free nucleic acids, and for the selective adsorption of nucleic acid-binding proteins, some DNA- and RNA-polymerases, or of nucleases. [Affinity Chromatography on Columns Containing Nucleic Acids. FEBS Lett. *88*, 161—166 (1978); 68 references]

[Rd 26 IE]

BOOK REVIEWS

Catalysis. Vol. 1. Senior Reporter: *C. Kemball*. Specialist Periodical Reports. The Chemical Society, London, 1977. xiv, 425 pp., numerous figs., bound, DM 137.70.

This book starts a new series on "Catalysis" under the general heading of Specialist Periodical Reports. The volume contains the following contributions: Catalysis on well-defined metal surfaces and non-metallic substrates (by *S. J. Thomson*); Reaction of hydrocarbons on alloys and bimetallic catalysis (by *R. L. Moss*); Catalysis on faujasitic zeolites (by *R. Rudham* and *A. Stockwell*); Catalytic properties of aluminas for reactions of hydrocarbons and alcohols (by *C. S. John* and *M. S. Scurrell*); Selective oxidation of hydrocarbons over mixed oxide catalysts (by *R. Higgins* and *P. Hayden*); Reactions on sulphide catalysts (by *P. C. H. Mitchell*); Ziegler polymeriza-

tion (by *A. D. Gaunt*); Olefin metathesis (by *J. J. Rooney* and *A. Stewart*); The homogeneous catalytic activation of C—H bonds (by *G. W. Parshall*); and Homogeneous catalysis involving carbon monoxide (by *P. J. Davidson, R. R. Hignett* and *D. T. Thomson*). The literature is covered up to the middle of 1976. The book gives a very good description of the subject and the research results in the fields specified, so that it is highly suitable both for experts and for chemists wishing to gain an insight into the subject. It deserves a wide readership among chemists, in higher education, and in industry. We can therefore look forward to the sequels with confidence. However, it is necessary to disperse some doubt about the need for this publication side by side with series having a similar orientation.

The book is well presented and is good value.

H. Kropf [NB 430 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Occupational Health and Safety Concepts—Chemical and Processing Hazards—. By *G. R. C. Atherley*. Applied Science Publishers Ltd., London 1978. xii, 408 pp., bound, $ 53.00.—ISBN 0-85334-742-5

Arzneimittelrecht von A—Z. By *D. Müller-Römer*. Otto Hoffmanns Verlag, Neu-Isenburg 1978. 471 pp., paperback, DM 48.—.—ISBN 3-87347-025-X

Chemistry and Biology of Thrombin. Edited by *R. L. Lundblad, J. W. Fenton, II*, and *K. G. Mann*. John Wiley & Sons, New York 1977. xii, 564 pp., bound, $ 14.20.—ISBN 0-250-40160-6

Structure and Stability of Salts of Halogen Oxyacids in the Solid Phase. By *F. Solymosi*. John Wiley & Sons, London 1977. 467 pp., bound, £ 15.00.—ISBN 0-471-81275-7

X-Ray Spectrometry. Practical Spectroscopy Series, Vol. 2. Edited by *H. K. Herglotz* and *L. S. Birks*. Marcel Dekker, New York 1978. xi, 518 pp., bound, $ 49.50.—ISBN 0-8247-6625-3

Physikalische Chemie und Biophysik. By *G. Adam, P. Läuger*, and *G. Stark*. Springer-Verlag, Berlin 1977. ix, 465 pp., paperback, DM 38.—.—ISBN 3-540-08419-3

Organische Komplexbildner mit variablem Abstand der Liganden. By *H. Stetter*. Research report of the Province Nordrhein-Westfalen, No 2713. Westdeutscher Verlag, Opladen 1978. iv, 112 pp., paperback, DM 22.—.—ISBN 3-531-02713-1

Molecular Structure by Diffraction Methods, Vol. 5. Senior Reporters: *L. E. Sutton* and *M. R. Truter*. The Chemical Society, London 1977. xiv, 440 pp., bound, DM 178.50.—ISBN 0-85186-547-X.—A volume of the series "Specialist Periodical Reports"

Inelastic Ion-Surface Collisions. Edited by *N. H. Tolk, J. C. Tully, W. Heiland*, and *C. W. White*. Academic Press, New York 1977. ix, 352 pp., bound, $ 19.00.—ISBN 0-12-703550-8

Treatise on Analytical Chemistry. Part III. Analytical Chemistry in Industry. Vol. 4. Edited by *I. M. Kolthoff, Ph. J. Elving*, and *F. H. Stross*. John Wiley & Sons, New York 1977. xxiii, 686 pp., bound, $ 50.00.—ISBN 0-471-02765-0

Fourier Transform Infrared Spectroscopy. Applications to Chemical Systems. Vol. 1. Edited by *J. R. Ferraro* and *L. J. Basile*. Academic Press, New York 1978. viii, 311 pp., bound, $ 25.00.—ISBN 0-12-254101-4

Analysis of Foods & Beverages. Headspace Techniques. Edited by *G. Charalambous*. Academic Press, New York 1978. xiv, 394 pp., bound, $ 21.00.—ISBN 0-12-169050-4

Inorganic Chemistry Concepts. Vol. 2. Magnetic Properties of Transition Metal Compounds. By *R. L. Carlin* and *A. J. van Duyneveldt*. Springer-Verlag, Heidelberg 1977. xv, 264 pp., bound, DM 44.—.—ISBN 3-540-08584-X

The Chemistry of Nonaqueous Solvents. Vol. VB. Acidic and Aprotic Solvents. Edited by *J. J. Lagowski*. Academic Press, New York 1978. xvi, 360 pp., bound, $ 36.50.—ISBN 0-12433841-0

Organometallic Polymers. Edited by *C. E. Carraher, Jr., J. E. Sheats*, and *C. U. Pittman, Jr.* Academic Press, New York 1978. xiv, 353 pp., bound, $ 18.50.—ISBN 0-12-160850-6

Thermodynamik. Grundlagen und Anwendungen in der Allgemeinen Chemie. By *R. Reich*. "taschentext" 62. Verlag Chemie/Physik-Verlag, Weinheim 1978. xxii, 291 pp., paperback, DM 24.—.—ISBN 3-527-21065-2 (Verlag Chemie); 3-87664-565-4 (Physik-Verlag)

Kirk-Othmer: Encyclopedia of Chemical Technology. Vol. 1. A to Alkanolamines. John Wiley & Sons, London 1978. xxix, 967 pp., bound, £ 50.00.—ISBN 0-471-02037-0

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Perfluoro Compounds as Blood Substitutes

By Jean G. Riess and Maurice Le Blanc[*]

Inconceivable as it is, it has been proved that animals can survive after having had their blood massively or even totally replaced by emulsions of perfluorinated compounds in salines. "Bloodless" rats charged with an emulsion of perfluorotri-*n*-butylamine survived a five hour period in an atmosphere containing 50% oxygen and 50% carbon monoxide, *i.e.* in conditions where the transport of oxygen by the red cells is entirely blocked. This review discusses: 1) the experiments which have demonstrated the capability of blood substitutes based on perfluorinated compounds to sustain life; 2) the characteristics and preparation of the relevant perfluoro compounds and the production and handling of their emulsions; 3) their "physiology", *i.e.* toxicity, life-span in the blood-stream, effect on the organs and their functions, and excretion properties. Obstacles remaining to be overcome in order to provide a safe blood substitute for medical practice include the availability of numerous series of well-defined pure and inert perfluorinated chemicals, the production of stable emulsions, the optimization of fluid balance, and the attainment of reasonable excretion rates. The accent is placed upon the role of the chemist in the progress of this research.

1. Introduction

Blood transfusion has become an everyday, life-saving measure, and there is a chronic shortage of blood, plasma, albumin, and other blood products to meet annually increasing demands[1]. Thus there is no doubt that there is a need for blood, but one may ask the question whether there is a need for *artificial* blood, and we must face the fact that if the answer is Yes, it is in large part because of the insufficient social concern of the public with respect to blood donation.

A satisfactory artificial blood would have some properties enabling it to supplant natural blood. For one thing, it would be universal—there would be no problems of hemocompatibility, and therefore no need for typing and crossmatching. Artificial blood could be conserved for unlimited periods; it would be available at will; the risk of transmission of diseases such as hepatitis, which is becoming seriously high, would be eliminated; the delicate and costly collecting, packaging, handling, storing, and distribution of natural blood, which is a highly perishable material, would be eliminated; furthermore it would make life-saving by transfusion possible in countries which are not yet equipped for the handling and distribution of natural blood. Moreover, many other applications have been suggested[2], both in therapy and in biomedical experimentation, which cannot be performed with natural blood. The principal potential uses of perfluorinated compound-based blood substitutes will be briefly summarized in Section 5.1.

This article is intended to survey research on blood substitutes using perfluoro compounds[*] as oxygen carriers, a startling and unforeseen application of these compounds. Several brief reviews or accounts on this topic[3–7] as well as the

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[*] The perfluorinated compounds used in this research field have often been rather loosely designated fluorocarbons, even when they contained some oxygen, nitrogen, or hydrogen atoms. We will in general call them perfluorinated or perfluoro compounds, and following the ACS recommendation [16] use the prefix "*F*" to indicate that a given compound is perfluorinated. For example, perfluorodecalin will be written "*F*-decalin". Any hydrogen atoms present will be indicated by the prefix "hydro".

proceedings of three state-of-the-art symposia[8] are already available. Since progress in the field is highly dependent on the availability of the relevant perfluoro compounds, the chemist's role in this research will be particularly emphasized in the present review. Its scope will be essentially limited to the preparation and uses of emulsions of perfluoro compounds as blood substitutes. Other solutions to the problem of blood replacement, such as the use of stroma-free hemoglobin[9], cross-linked hemoglobin[10], or synthetic oxygen-binding chelates[11], and other biomedical applications of perfluoro compounds, especially in liquid respiration[12] and lung lavage[13], in extracorporeal blood oxygenation[14] or as radiopaque[15], will not be considered here.

2. The Capability of Perfluoro Compound-Based Blood Substitutes of Sustaining Life

It may all have started in 1962 with *Kylstra*'s communication "Of Mice as Fish", when he showed that mice could be kept alive when immersed in hyperbaric solutions of oxygen in aqueous saline solutions[17]. Then, in 1966, *Gollan* and *Clark* found that the same result could be obtained under normal atmospheric pressure by using perfluoro compounds instead of water[18]. *Howlett et al.* had used these compounds as blood oxygenators in 1965[19]. Figure 1 shows a mouse in a breaker filled with perfluoro compounds saturated with oxygen. It is actually breathing the liquid.

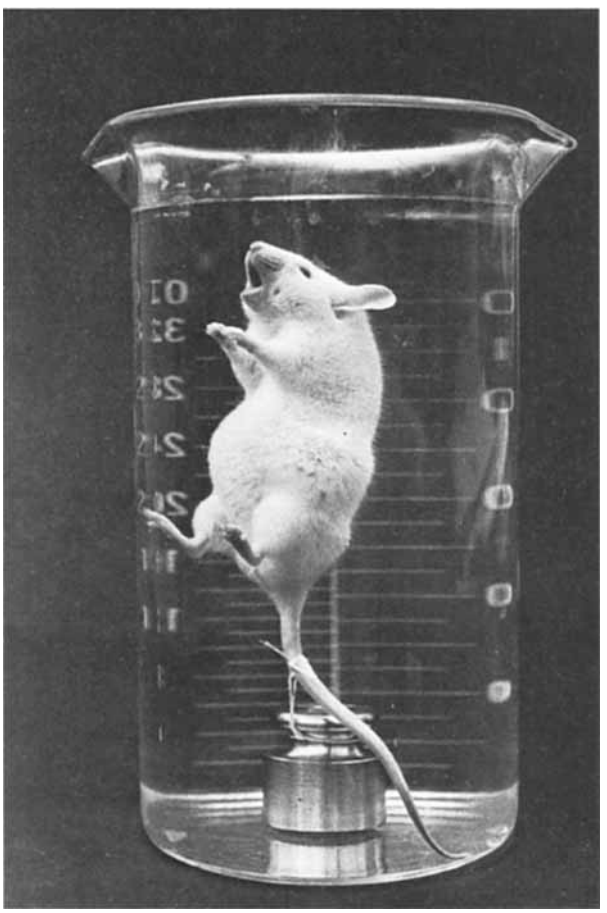
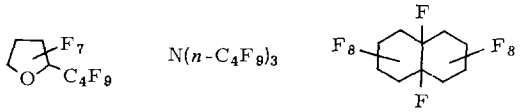


Fig. 1. Mouse breathing a liquid perfluoro compound saturated with oxygen (by courtesy of Prof. *L. C. Clark, Jr.*, Department of Pediatrics, University of Cincinnati).

Gollan and *Clark* were also the first to attempt to use perfluorochemicals instead of blood to supply an organ with oxygen, when they showed that the isolated heart of a rat would continue to contract vigorously when perfused with a perfluoro compound saturated with oxygen[20]. However, the perfusion had to be alternated every hour with that of oxygenated diluted blood in order to assure the supply of mineral salts, which are insoluble in the perfluoro compounds.

Very shortly afterwards, in 1967, considerable progress was made when *Sloviter et al.* replaced the pure perfluoro compound by an emulsion of this compound in a plasma[21]. In this way they solved the problem of the transport of mineral salts and metabolites. The preparations they used were rather crude emulsions (2—3 μm in diameter) containing 20% of FX-80, a perfluoro compound mixture marketed by the 3M Company, whose main constituent is *F*-2-butyltetrahydrofuran *(1)* emulsified in a plasma constituted by a Krebs-Ringer bicarbonate buffer solution with bovine serum albumin as



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

a surfactant. The ability of these emulsions to deliver oxygen to the tissues was tested on isolated rat brain, and compared with that of a suspension of erythrocytes in the same plasma, and with that of the plasma alone. The spontaneous electric activity of the brain (more than 5 μV) persisted for more than 2 hours with the plasma loaded with red cells and with the emulsion of perfluoro compound, compared to less than 5 minutes with the plasma alone (Fig. 2).

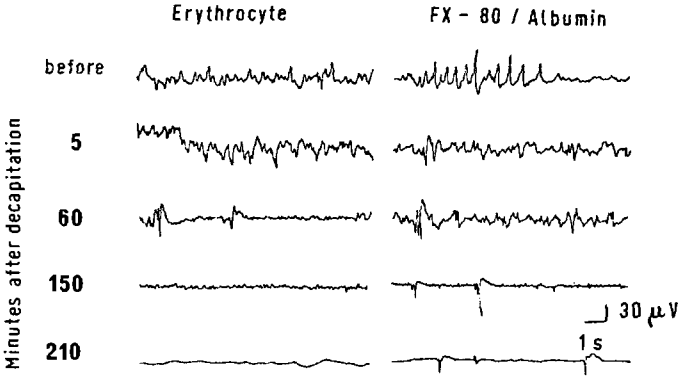


Fig. 2. Comparison of the spontaneous EEG activity of isolated rat brains perfused with an erythrocyte suspension and with an emulsion of the perfluorochemical FX-80 (from ref. [21]).

Considering how vulnerable the brain is to a shortage of oxygen—electric activity ceases if the perfusion is interrupted for just 30 seconds—it can be concluded that in these experiments the emulsion of perfluoro compound assured the oxygen supply just as well as a suspension of red cells. The curves for glucose consumption and lactate production were almost the same for both types of perfusion fluids, which indicates that the emulsion also maintained the metabolic activity of the brain.

In 1968, *Geyer* reported the first *complete* replacement of the blood of rats by an emulsion of FC-47, another 3M product whose main constituent is *F*-tri-*n*-butylamine *(2)*

with Pluronic F-68, a polyethylene oxide-polypropylene oxide block polymer, as surfactant. However, survival of the animals was limited to a few hours[22–25].

Another significant experiment by *Sloviter*'s team showed that mice whose blood contained 10 to 20% of emulsified FX-80 could survive for considerably longer times than controls in an atmosphere containing 4% carbon monoxide, *i.e.* in conditions in which the transport of oxygen by the red cells is almost completely inhibited by carbon monoxide[26].

By 1969 the aptitude of emulsified perfluorochemicals to supply oxygen to tissues, organs, and whole animals, including rats, mice, guinea pigs, frogs, rabbits, chickens, cats and dogs, had been established. However, the animals generally did not survive longer than a few hours. Then, from 1970 onwards, experiments started to be reported in which series of animals survived massive but still partial exchange perfusion with such emulsions[24, 25] and thereafter continued to live, grow, and develop, apparently normally. *Clark et al.* mention, for example, dogs that were perfectly healthy three years after having received a 25% emulsion of FC-47 in a posology of 50 ml/kg of body weight[27, 28]. Similar experiments, in which dogs survived the substitution of 80 to 85% of their blood, were reported by *Fujita et al.* in Japan[29].

The ability of perfluoro compounds to function as blood substitutes to sustain life was conclusively demonstrated when *Geyer*, in 1973, described experiments in which the blood of rats was progressively but *totally* replaced by emulsions containing 12% of FC-47, with subsequent survival of the animals[30, 31]. His experiments are shown schematically in Figure 3. The first stage is a perfusion during which the

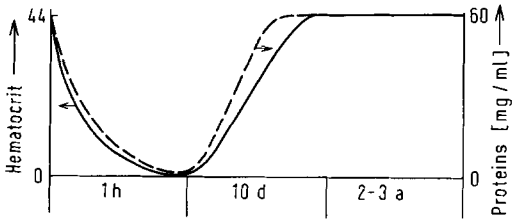


Fig. 3. Schematic view of the successive phases of *Geyer*'s total blood substitution experiments (from ref. [30]): exchange perfusion (1 h); regeneration phase (10 d); normal life-span (2—3 years).

hematocrit (the red cell content of blood) is brought down to less than 1 vol.%. In order to achieve this, *Geyer* perfused the animals under anesthesia with up to 30 times their normal blood volume (for a human being weighing 70 kg this would require about 160 l of emulsion). On awakening after perfusion, "bloodless rats" apparently behaved in a normal manner, and immediately resumed eating, drinking, urinating, defecating, building nests, and so on. After about 7 to 10 days, the plasma protein and hematocrit levels were back to the normal range. The animals continued to grow and develop without apparent abnormality throughout their usual life-span.

Unfortunately, however, it was found that *F*-tri-*n*-butylamine was retained for long periods, maybe the entire lifetime, in the body of the animals, mainly in the liver. Therefore the independent discovery by *Clark et al.*[32] and by *Naito et al.*[33] that some perfluorocompounds such as *F*-decalin *(3)* are excreted from the body much more rapidly than others was an important step forwards.

Recently, experimentation has begun on monkeys. A conscious rhesus monkey appeared to be completely unaware of the fact that about one third of his blood volume was being replaced by an *F*-decalin/Pluronic F-68 emulsion[34]. His pulse did not change appreciably, and according to the authors he apparently suffered no measurable physiological, chemical, or psychological perturbations. He was still alive over a year later. Eight out of a series of ten rhesus monkeys survived removal and dilution of about half their blood, followed by infusion with a 10% *F*-decalin emulsion, and appeared to be in good health (the two others died from surgical accidents). There were no significant changes in about 20 blood components analyzed[35]. Considerable variability between monkeys was noted in the amount of perfluoro compound they sequestered in their liver and spleen, and in the rate at which it left them; the half-life of *F*-decalin in the liver is probably around two weeks. Morphological studies showed no damage or residual effects of its temporary occupation of the liver.

Although all the above experiments were devised with the ultimate aim of achieving artificial blood substitutes, their significance is widely different, and must be critically evaluated. Some, such as the isolated brain perfusion experiments or the protection of mice against poisoning by carbon monoxide, show that the emulsions can assure oxygen transport and replace the erythrocytes in this one function. Those which led to survival after massive but still partial blood substitution in animals show that massive doses of the alien perfluorochemicals can be tolerated by the organism, but they do not really demonstrate that the oxygen supply is assured by the perfluorocompounds, since it is known that 10 to 20% of the erythrocytes suffice to sustain life provided the blood volume, osmotic and oncotic[*] pressure, and flow characteristics of blood are maintained. Thus only those experiments which led to survival of animals after complete blood substitution, so that there was no opportunity of relying on residual normal blood constituents, really demonstrated that the emulsions can function as blood substitutes.

In this respect one of the most significant experiments recently performed by *Geyer* was to assure the survival of his "bloodless rats" after they had been breathing an atmosphere containing 10% of carbon monoxide for 20 hours[4] (Fig. 4),

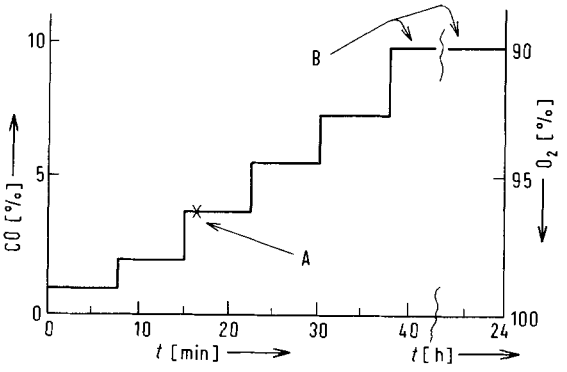


Fig. 4. Comparison of the survival of "bloodless" and normal rats in an atmosphere consisting of 10% CO/90% O_2 (from ref. [4]). A, controls dead; B, "bloodless" rats still alive and active.

[*] The oncotic pressure is the osmotic pressure due to the proteins.

or even an atmosphere containing 50% carbon monoxide for 5 hours[36]. The animals were subsequently returned to a nitrogen/oxygen atmosphere, and survived. These are conditions in which not only any residual red cells, but also the new cells which are continuously produced by the animal, are immediately blocked by carbon monoxide. This definitely proves that the emulsified perfluorochemical had assured the oxygen supply entirely for at least 24 hours. The survival of the animals afterwards moreover seems to mean that carbon monoxide does not act as a poison for tissues and organs.

3. Synthesis of the Relevant Perfluoro Compounds and Processing of Blood Substitutes

3.1. Requirements of an Artificial Blood Substitute

An artificial blood substitute must meet the following requirements:

1) It must maintain blood volume, osmotic and oncotic pressures, and flow characteristics close to those of normal blood; it must also assure proper pH control. These are in fact the requirements to be met by any effective *plasma* substitute.
2) It must assure proper O_2 and CO_2 transport and exchange.
3) It must be chemically inert, not react with O_2 or CO_2, and not develop toxic impurities during its functioning.
4) It may not interfere with any component of natural blood, not cause any irreversible damage no tissues and organs, nor perturb their normal functioning.
5) It must allow regeneration of red cells, proteins, and the other blood constituents at a reasonable rate.
6) It must allow for normal survival, growth, and development after complete blood substitution.
7) It must eventually be excreted from the body.

A substitute which fulfils these conditions is much more than a plasma, since it transports oxygen, *i.e.* replaces the erythrocytes in this function; but this of course constitutes only a part of the multiple and complex operations of transport, regulation, clotting, and defense performed by natural blood. In this respect use of the term "artificial blood" for a medium which satisfies only these requirements is certainly an overstatement.

3.2. Solubility and Availability of Oxygen in Perfluoro Compounds

Perfluoro compounds were chosen as gas carriers because they dissolve large amounts of gases[37–42], they are chemically inert, and they are generally atoxic[41,43]. However, it should be remembered that the requirements listed in Section 3.1 must be met, not by the perfluoro compound as such, but by its emulsions. The amount of oxygen dissolved can be measured by VPC[37b] or by the conversion of Fe^{2+} into Fe^{3+} followed by titration using $TiCl_3$[44].

Table 1 compares the solubility of O_2 and CO_2 in plasma, blood, several commonly-used perfluoro compounds, and two emulsions which are now commercialized for biomedical experimentation (Fluosols)[41]. One sees that the plasma alone dissolves 2 vol-% of O_2, the pure perfluorocompounds 40 to 50%, and the commercially available emulsions 7 to 9%. These emulsions thus dissolve roughly four times as much oxygen as a plasma. The direct comparison of these figures where blood and perfluoro compounds are concerned has in fact little meaning, since the mechanisms by which the oxygen is fixed, and therefore the *availability* of this oxygen, are entirely different.

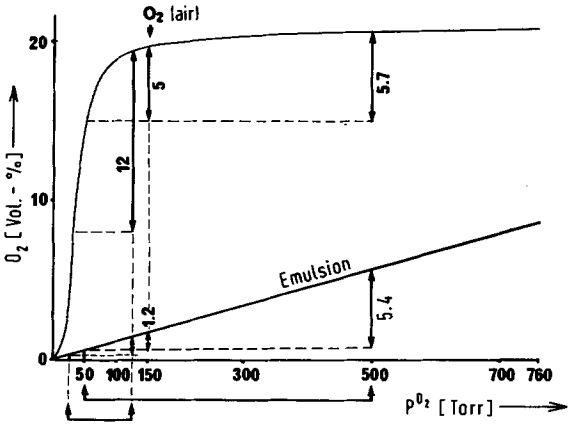


Fig. 5. Comparison of oxygen content and availability in blood and in a 30% emulsion of *F*-tri-*n*-butylamine (FC-43)/Pluronic F-68.

Figure 5 illustrates this point: in this figure the dissolved or fixed oxygen volume is plotted against oxygen partial pressure: in blood, oxygen is coordinated to the hemoglobin iron atom, and the oxygen uptake curve has an S-shape that rapidly levels off to a plateau, while the volume of oxygen dissolved in the emulsions of perfluoro compound increases linearly to a first approximation according to Henry's law.

Under biological conditions, the O_2 content of the arterial blood is about 20 vol-%; it drops to about 15 vol-% for venous blood after uptake of the oxygen by the tissues. It may be seen from Figure 5 that natural blood can easily release these 5 vol-% of O_2 when the animal breathes air. This corresponds on the curve to a drop in pO_2 from 150

Table 1. Gas solubilities (vol-% under 1 bar).

	O_2		CO_2		O_2 from air		Ref.
	25°C	37°C	25°C	37°C	25°C	37°C	
Plasma		2.4		67			[38]
Blood		20		50		20	[38]
F-Tributylamine *(2)*	38.9	40.3	152	142	10.3	10.4	[39]
F-Butyltetrahydrofuran *(1)*	48.8	48.5	192	160	12.6	11.7	[39]
F-Decalin *(3)*	40.3			134 [a]	8.6		[37a]
Fluosol-43	9.3	8.7	84	72	1.9	1.7	[41]
Fluosol-DC	8.1	7.9	86	62	1.6	1.6	[41]

[a] Emulsified with Pluronic F-68 in water [40].

torr—the partial pressure of oxygen in air—to 50 torr. When the same variation in pressure is applied to the emulsion it releases only about 1.2 vol-% of O_2, that is 4 times less. In order to be as effective as blood, the emulsion has to operate at a pressure drop of *ca.* 400 torr. The difference in behavior of the two systems is even more vital in the case of a shortage of oxygen: in a rarefied atmosphere, blood can still supply the oxygen demand, for example, about 12 vol-% of O_2 are released during the same pressure drop but from 125 to 25 torr, while the emulsion still releases only 1.2 vol-% of O_2. All this means that blood substitution experiments using perfluoro compounds have to be made with animals breathing oxygen-rich atmospheres.

Furthermore, a recent report shows that the emulsions of perfluoro compounds depress the O_2 uptake of isolated tissues, but that this depression can be overcome by the use of O_2 levels approaching saturation. This also suggests that high levels of inspired O_2 will have to be maintained when using perfluoro compound-based blood substitutes[50b].

3.3. Problems Relating to the Availability and Purity of the Relevant Perfluoro Compounds

An early and still serious drawback in this research concerns the availability of the relevant fluorochemicals. Those whose use in emulsion form as blood substitutes has been reported

Table 2. Perfluoro compounds tested as blood substitutes.

Perfluoro compound	Intravenous acute toxicity of emulsions	Emulsion stability and control	Retention in the body	Massive perfusion of animals	Total blood substitution [a]	Studies of organs and blood after i.v. perfusion	Perfusion of isolated organs	Abbreviations and commercial names
F-Alkanes, cycloalkanes, and alkenes								
n-C_8F_{18}	[27, 28]	[27, 69, 71]						
n-$C_{10}F_{22}$	[27]	[27]						
n-$C_{10}F_{21}H$	[27]	[27]						
n-$C_8F_{17}C_2H_5$	[27]				[48]			(Produits Chimiques Ugine Kuhlmann)
n-$C_{10}F_{21}C_2H_5$		[27]						
n-$C_8F_{17}CH{=}CH_2$		[71]						
n-$C_4F_9CH{=}CH$-n-C_4H_9		[71]						[105b, c]
n-$C_6F_{13}CH{=}CH$-n-C_6F_{13}		[71]			[124*]			
n-$C_8F_{17}CH{=}CH$-n-C_4F_9		[71]						
F-Methyladamantane	[88]	[88]	[88]					PFMA (Imperial Smelting)
F-Dimethyladamantane	[27, 28, 88]	[27, 35, 88]	[88]					PFDMA (Imperial Smelting)
F-Methyldecalin	[27, 28]	[68]	[28, 31, 88, 89]	[89]	[93*]	[55]	[62, 77]	MFD, PP9 (Imperial Smelting)
F-Decalin	[28, 31, 35, 88]	[27, 31, 35, 56, 57, 68]	[27, 31, 35, 41, 43, 58, 61, 72, 88, 89]	[31, 34, 35, 60, 61, 89]	[60, 61]	[27, 31, 34, 35, 55, 56, 72]	[62, 77]	FDC, PP5 (Imperial Smelting)
F-Ethers and related compounds								
$(CF_3)_2CFOC_6F_{13}$		[70]						P-12F, caroxin F (Allied)
$(CF_3)_2CFO(CF_2)_4OCF(CF_3)_2$	[28]	[70]	[28, 91]	[91]				P-1D, caroxin D (Allied)
$(CF_3)_2CFO(CF_2)_8OCF(CF_3)_2$	[28, 45]		[28, 45, 89]	[45, 89]		[50]		P-11D (Allied)
$CF_3CHF\left[OCF_2{-}CF(CF_3)\right]_n{-}F$ $n=1$	[24]							E_1
2	[24, 45]		[45]					E_2
3	[24, 28]		[28]	[91]				E_3
4	[24, 28, 45]	[47, 49]	[31, 45, 47, 49]	[91]		[50]		E_4 (Freons E (Du Pont))
5	[24]							E_5
9	[45]		[45]					E_9
F-Isopentyltetrahydropyran		[46]	[46]			[55]		FTC (Dainippon Ink, 3M)
F-Butyltetrahydrofuran	[24, 51, 84]	[27, 67, 69]		[26, 91]		[51, 84]	[21, 53, 62, 63, 65, 76, 77, 80, 81, 86, 96]	FC 75, FC 80, FX 80 (3M) (FC 77, FC 78)?
$F(CF_2CF_2CF_2O)_nCCF_2CF_3$ (O)	[28]							Fomblin Y-04 (Montedison)
F-Amines								
F-N-Methyldibutylamine		[46]	[46]			[55]		FBA (Dainippon Ink, 3M)
F-N-N-Diethylcyclohexylamine		[46, 47, 68]	[46, 47]			[55]		FDEA (Dainippon Ink, 3M)
F-Tri-n-butylamine	[24, 28, 45, 51, 54, 84, 87, 88, 94]	[24, 27, 35, 41, 52, 56, 57, 59, 66, 67, 69, 71, 72, 73]	[27, 28, 31, 41, 88, 89]	[24, 25, 26, 31, 52, 69, 89, 90, 91, 95]	[24?, 25, 30*, 36*?, 64*, 69*, 85, 92*, 95]	[27, 51, 52, 55, 56, 72, 73, 84, 90]	[74, 75, 78, 79, 81, 82, 83]	FC 43, FC 47 (3M), PFTBA

[a] *, successful; ?, questionable.

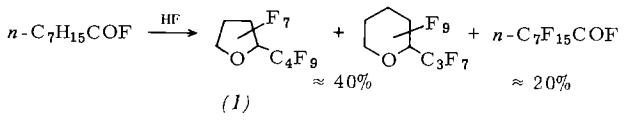
are listed in Table 2. A few other compounds have occasionally been mentioned, especially in the patent literature but no precise results on them have been made available. As can be seen, most of those Table 2 have been tested for acute toxicity only (generally by intravenous injection of small amounts), and the number of compounds that have been tested in any depth is still very limited. Moreover, their structures are disparate, and there were generally no homogeneous series available. First a branched cyclic ether was used, then a tertiary amine, some ethers, then saturated bicyclic fluorocarbons, and so on. This poses a problem, since such essential properties as their stability in emulsions, the physiological response of the organism to injection, and the rapidity of their excretion have been found to differ profoundly from one compound to another. Thus it is primordial that diverse sorts of homogeneous series should be made available if one is to establish which are the most favorable structural and physicochemical characteristics for this use.

This situation is primarily due to the relatively large quantities of compounds required for experimentation. Thus one was forced to use compounds that had already become industrially accessible.

This brings us to another serious difficulty, which arises from the insufficient purity, chemical definition, and reproducibility of these materials, which until recently were manufactured for completely different purposes, for which the standards of purity have nothing in common with those required for biomedical experimentation. This is particularly so with electrochemically produced materials, which are generally complex mixtures, whose composition is not even reproducible from one batch to the next. It is necessary to stress here the ambiguity that has therefore long hung over the exact composition of the substances used in the biomedical experiments, and to insist on the need to devise more specific, unequivocal routes allowing the synthesis of purer, better-defined compounds.

3.4. Synthesis of the Perfluoro Compounds Used in Blood Substitution

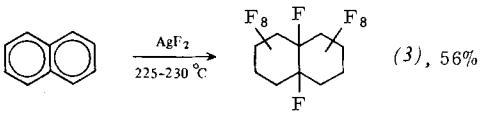
The principal routes that are employed for the preparation of the basic materials used so far in the preparation of blood substitutes will be briefly recalled. The most important one is electrochemical fluorination in anhydrous hydrogen fluoride. It was used in the preparation of the first perfluoro compounds tested in blood substitution (FX-80[97] and FC-47[98]). However, this method, which replaces a C—H bond (*ca.* 90 kcal/mol) by a C—F bond (100—120 kcal/mol), and therefore releases considerable amounts of energy, is very brutal and is generally accompanied by heavy degradation. For example, electrolysis of octanoyl fluoride with hydrogen fluoride gives the product FX-80 which, according to the patent, may consist largely of the following components:



(1)

Light fluorocarbons, lower cyclic homologs having shorter side chains, and telomerization products are also present. Some of the samples used in the early experiments showed up to 16 constituents detectable by VPC[99].

The preparation of *F*-decalin *(3)* exemplifies another general route to perfluoro compounds, which uses metal fluorides as fluorinating agents. Thus *F*-decalin was first obtained by treating naphthalene with silver fluoride[100].

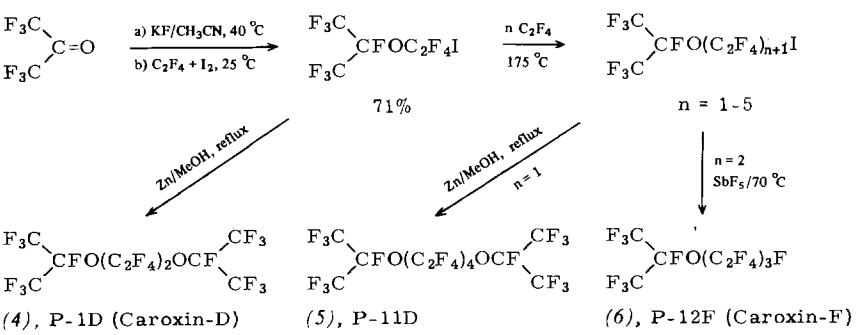


(3), 56%

The commercial product, PP5 manufactured by the Smelting Company, is probably obtained with cobalt trifluoride as a fluorinating agent. This is again a very drastic method which results in complex mixtures: the crude commercial products have boiling points ranging from 53 to over 93 °C, and the lighter fractions were shown to be definitely toxic[27]. Even the *F*-decalin purified by spinning band distillation, and commercialized by the Green Cross Corporation for medical purposes, still contains several impurities besides *cis*- and *trans*-*F*-decalin[41].

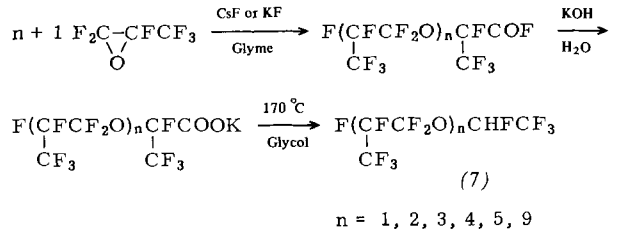
More recently, new techniques have been devised which allow a better control of the direct fluorination of organic compounds by elemental fluorine[101]. For example, adamantane was converted into 1-hydro-*F*-adamantane in 44 % yield using helium-diluted fluorine at −78 °C, and 2,2,4,4-tetramethylpentane was converted into 3-hydro-*F*-tetramethylpentane in *ca.* 60 % yield[102]. This certainly opens up interesting prospects for the synthesis of better defined perfluoro compounds.

The perfluoroisopropyl ethers *(4)*, *(5)*, and *(6)* are on the other hand examples of perfluoro compounds obtained by specific chemical routes. They are produced in 99% purity by Allied Chemical Corp.[103].



(4), P-1D (Caroxin-D) *(5)*, P-11D *(6)*, P-12F (Caroxin-F)

Du Pont's Freons E *(7)*, which have also been tested for blood substitution, are also produced by chemical routes[104].



$$n + 1\ F_2C\!-\!CFCF_3 \xrightarrow[\text{Glyme}]{\text{CsF or KF}} F(CFCF_2O)_nCFCOF \xrightarrow[H_2O]{\text{KOH}}$$

$$F(CFCF_2O)_nCFCOOK \xrightarrow[\text{Glycol}]{170\,^\circ C} F(CFCF_2O)_nCHFCF_3$$

(7)

n = 1, 2, 3, 4, 5, 9

At present, various efforts are being made to produce compounds that are specifically fitted to serve as gas carriers for blood substitutes. These efforts are directed either towards assuring better control of electrochemical fluorination or of direct fluorination by elemental fluorine, or towards the use of selective chemical routes, starting from simpler but already perfluorinated starting materials.

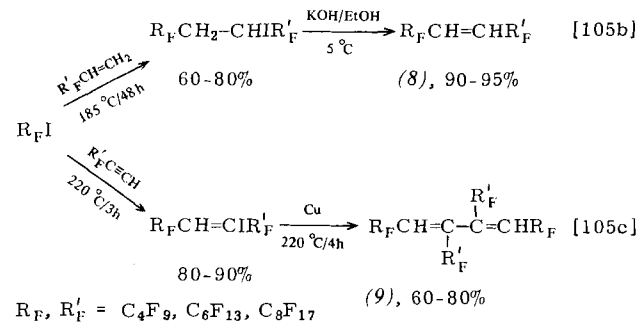
Our own approach to the design of such tailor-made compounds belongs to the latter category, and is based on the following guidelines[105]:

1) The starting materials are industrially available perfluorinated building blocks such as the perfluoroalkyl iodides $C_nF_{2n+1}I$ ($n = 4, 6, 8$), which are produced in satisfactory purity by Produits Chimiques Ugine Kuhlmann by telomerization of tetrafluoroethylene with perfluoroethyl iodide.

2) Several perfluoroalkyl groups are linked together into bundles by specific chemical routes.

3) Heteroatoms, such as oxygen and nitrogen, which were thought to be responsible for the retention of the compounds in the liver[89], are avoided.

4) Homologous series of compounds are prepared, in order to permit the stepwise optimization of such crucial parameters as vapor pressure or viscosity. Examples of such series are the bis-*F*-alkylethanes *(8)* and the tetrakis-*F*-alkylbutadienes *(9)* which were obtained by the following routes:



$$R_FCH_2\!-\!CHIR'_F \xrightarrow[5\,^\circ C]{KOH/EtOH} R_FCH{=}CHR'_F \quad [105b]$$

R_FI + $R'_FCH{=}CH_2$ (185 °C/48 h): 60–80%

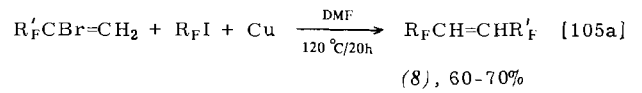
R_FI + $R'_FC{\equiv}CH$ (220 °C/3 h): *(8)*, 90–95%

$$R_FCH{=}CIR'_F \xrightarrow[220\,^\circ C/4h]{Cu} R_FCH{=}C(R'_F){-}C{=}CHR_F \quad [105c]$$

80–90% *(9)*, 60–80%

R_F, R'_F = C_4F_9, C_6F_{13}, C_8F_{17}

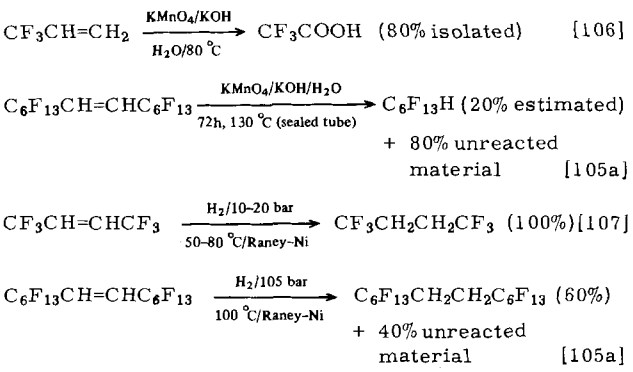
It is noteworthy that the bis-*F*-alkylethenes *(8)* can also be obtained by allowing the 1-iodo-*F*-alkanes to react with 1-*F*-alkyl-1-bromoethene in the presence of copper powder.



$$R'_FCBr{=}CH_2 + R_FI + Cu \xrightarrow[120\,^\circ C/20h]{DMF} R_FCH{=}CHR'_F \quad [105a]$$

(8), 60–70%

The chemical inertness of these bis-*F*-alkylethenes is illustrated by the experimental conditions required for their oxidation or reduction, which are much more drastic than those required when R_F is CF_3.



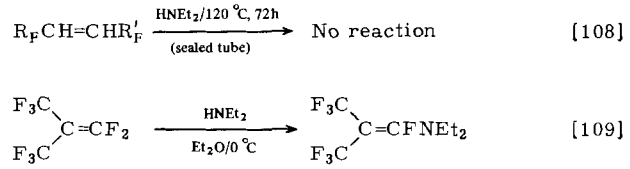
$$CF_3CH{=}CH_2 \xrightarrow[H_2O/80\,^\circ C]{KMnO_4/KOH} CF_3COOH \text{ (80\% isolated)} \quad [106]$$

$$C_6F_{13}CH{=}CHC_6F_{13} \xrightarrow[72h,\ 130\,^\circ C\ \text{(sealed tube)}]{KMnO_4/KOH/H_2O} C_6F_{13}H \text{ (20\% estimated)} + \text{80\% unreacted material} \quad [105a]$$

$$CF_3CH{=}CHCF_3 \xrightarrow[50\text{–}80\,^\circ C/\text{Raney-Ni}]{H_2/10\text{–}20\ bar} CF_3CH_2CH_2CF_3 \text{ (100\%)} \quad [107]$$

$$C_6F_{13}CH{=}CHC_6F_{13} \xrightarrow[100\,^\circ C/\text{Raney-Ni}]{H_2/105\ bar} C_6F_{13}CH_2CH_2C_6F_{13} \text{ (60\%)} + \text{40\% unreacted material} \quad [105a]$$

Their lack of reactivity towards primary or secondary amines contrasts with the behavior of the completely fluorinated alkenes, which easily add amines with subsequent elimination of hydrogen fluoride below room temperature.



$$R_FCH{=}CHR'_F \xrightarrow[\text{(sealed tube)}]{HNEt_2/120\,^\circ C,\ 72h} \text{No reaction} \quad [108]$$

$$(F_3C)_2C{=}CF_2 \xrightarrow[Et_2O/0\,^\circ C]{HNEt_2} (F_3C)_2C{=}CFNEt_2 \quad [109]$$

3.5. Crucial Characteristics of the Perfluorochemical Emulsions

All the perfluoro compounds tested so far are liquids, and have to be used in an emulsified form because: 1) pure compounds would cause immediate embolism[110]; 2) this solves the problem of the simultaneous transport of oxygen, mineral salts, and metabolites; 3) provided they are not too fine, the rheological properties of emulsions are closer to those of the continuous phase, and thus closer to those of the plasma.

The preparation and characteristics of the emulsions soon turned out to be a crucial problem. Without apparent reason some emulsions were good and others were toxic, and this often led different research groups to reach contradictory conclusions[53, 65].

An emulsion is a complex multi-parameter system[111], whose properties depend not only on its components (perfluoro compound, saline aqueous phase, surfactants) and their proportions, but also on the particle size and size distribution. The size of the liquid particles is an all-important factor, not only because it influences the stability of the emulsion, the surface area available for gaseous exchange, and, as regards the finer ones, their viscosity, but also because in the body it largely determines their toxicity, the time the perfluoro compounds will spend in the blood stream, and perhaps the extent to which they are phagocytized and stored in certain organs.

There is a correlation between particle size and the toxicity of the emulsions: acute toxicity was found to increase rapidly with the proportion of particles larger than 0.4 μm[66]. An average particle size of less than 0.1 μm with no particle larger than 0.6 μm is now recommended[40]. Such particles are much smaller than erythrocytes (7—8 μm), but they are far more numerous, and the commonly used emulsions thus offer 150—300 times as much surface area for gaseous exchange. Emulsions having such small particle sizes are almost optically clear, *i. e.* transparent, but become milky-white with increasing particle size.

It is, of course, essential that the emulsions be stable, and that their particle size should not increase while they are in the bloodstream. The stability depends on the nature of the perfluoro compound. Thus, the *F*-decalin/pluronic emulsions are much less stable than the emulsions of *F*-tributylamine, *F*-dimethyladamantane, or Freon E3 with the same surfactant[28,40,57,62]. The stability of the *F*-decalin emulsions can be improved by addition of egg yolk phospholipids, D-sorbitol[57], and traces of a fatty acid salt[67] as surfactant[40,49]. However, the intravascular stability of this emulsion is limited[56], probably as a consequence of the faster elimination of the yolk phospholipids leading to insufficient coverage of the particles by the surfactant. On the other hand, it has been reported that some emulsions were more stable *in vivo* than *in vitro*[26]; this seems surprising and the true explanation probably lies in the rapid removal of coarser particles from the bloodstream *in vivo*.

The surface charge of the particles may be important and influence the rate at which they will be phagocytized. In addition the blood platelets which are negatively charged will tend to clump together on positively charged sites and may promote formation of thrombi[41,49,51,73,112].

3.6. Problems Relating to Emulsification

The preparation of the emulsions involves several difficulties. Firstly, one has to select a surfactant in the absence of valid guidelines for such a choice. Of the dozen surfactants mentioned in blood substitution experiments, only two have come to the fore, *viz.* the polyethylene oxide-polypropylene oxide block polymer Pluronic F-68[113] and phospholipids from egg yolk[67,68]. Pluronic F-68, which is most widely used, is also one of the first to have been tested. This appears to have been a stroke of luck, since no better one has been found since. Not only is it atoxic, inert, and excretable, but it does not cause hemolysis (in contrast to most surfactants), it acts as a mild anticoagulant[45], and it has the seemingly unique property among the surfactants of also behaving as an oncotic agent[30,111c]. A few other surfactants, such as amine *N*-oxides[47,114,70] have occasionally been mentioned, as well as some perfluoroalkylated surfactants[55,70,71,115].

The emulsification procedures can be roughly divided into two kinds: those which subject the sample to large amounts of energy and those which do not. To the first class belongs the most commonly used sonication procedure using ultrasonic vibration (*e.g.* 20 kHz, 1000 W)[3,64]. However, it has been found that sonication promotes the release of fluoride ions[28], implying that some molecules have been degraded to form new molecular and ionic constituents; this adds to the complexity of the mixtures and to the uncertainty surrounding their composition. Some sonication devices were even observed to release titanium particles into the emulsion[45].

Although the toxicity of these emulsions can subsequently be reduced (see Section 3.7) and the fluoride ions removed (note that much larger doses of fluoride can be injected into the blood stream and appear to be well tolerated)[48], it nevertheless seems essential to search for methods of emulsification that do not modify the chemical constitution of the compounds being tested.

A rather puzzling discovery is that the generation of fluoride ions can be almost completely repressed if the sonication is performed in a carbon dioxide atmosphere[64].

Another procedure for the production of almost colloidal emulsions in large quantities uses the Manton-Gaulin high pressure homogenizer. This method exploits shearing forces, and also subjects the materials to high doses of energy.

More recently attention has been focused on milder emulsification methods. The use of self-emulsifying systems has been proposed in which two different emulsifiers are present. One emulsifier is more hydrophilic while the other is more lipophilic; together they form fine emulsions that are stable in a chosen temperature range. Mixtures of perfluoroalkylated surfactants of type $R_F(C_2H_4O)_nH$, with an average $n \approx 3$ for the "fluorophilic" surfactant and $n \approx 12$ for the hydrophilic one, were used for this purpose[71]. However, the emulsions produced so far have proved to be rather toxic[48].

Another novel method which is claimed to give stable microemulsions under gentle conditions involves dissolution of the perfluoro compounds in a volatile propellant such as freon 113 ($CF_2Cl-CCl_2F$) and subsequent addition to the aqueous phase containing the surfactants (one of which is fluorinated). Upon gentle stirring, a micro-emulsion spontaneously develops and the mixture becomes transparent. The light solvent is then removed by evaporation[70].

Table 3. Composition of artificial blood substitute for total exchange perfusion (*Geyer*, 1973) [30].

Perfluorotributylamine FC-47	11.0–13.0 ml
Pluronic F-68 [a]	2.3–2.7 g
Hydroxyethyl starch	2.5–3.2 g
Glucose (when present)	0.1 g
NaCl	54 mg
KCl	32 mg
$MgCl_2$	7 mg
$CaCl_2$	10 mg
NaH_2PO_4	9.6 mg
Na_2CO_3	to pH 7.44
H_2O	to 100 ml
Penicillin, streptomycin, phenol red	

[a] Polyethylene oxide-polypropylene oxide block polymer.

Table 3 represents the composition of a typical blood substitute, as used by *Geyer* in his total blood substitution experiments[4,64]. Other compositions for substitutes and detailed experimental procedures may be found for example in references[40,41,57,61].

3.7. Emulsion Control and Standardization

The paramount importance of having properly defined emulsions, and hence the need for standardized and reproducible preparation procedures, is now fully recognized. Indeed, it is surprising that this point could have been overlooked for so long.

It has meanwhile been established that only some of the constituents of the early "toxic" emulsions are actually toxic. This follows from the fact that the toxicity of such emulsions could be reduced by a simple filtration[67], passage over an ion-exchanger[3,28], or dialysis[3,45]. The same applies to the Pluronics, which are essentially atoxic in the pure state but lead to various complications such as pulmonary edema and

hemorrhages when used without preliminary purification by passage through a Millipore filter[45, 52].

The perfluoro compounds are now carefully washed and distilled; the emulsification is sometimes optically monitored and the emulsions characterized by optical density curves; sonication, for example, is applied until a plateau in the optical density is observed[28], thus providing reproducible emulsification procedures for a given fluoro compound/surfactant combination. The stability of an emulsion can also be judged from the rate at which optical density increases with time. The particle size is determined by electron microscopy, or more conveniently by ultracentrifugal sedimentation[40, 59, 66]. The effect of the increase in viscosity at very small particle sizes on the flow characteristics can be counterbalanced by the addition of hydroxyethyl starch[30, 31]. The oncotic pressure is adjusted and controlled by osmometry[93]. The importance of the atmosphere has been recognized; a CO_2 atmosphere facilitates emulsification, suppresses foaming, and prevents fluoride ion formation[64]. The preparations are sterilized by heat[27, 40, 67, 68] (pasteurized in the case of the less stable emulsions) or by filtration through Millipore filters[64], and may be frozen for storage[57]. Two standardized commercial emulsions are now available from the Green Cross Corporation (Japan)[41][*].

More effort will have to be devoted to achieving a better control of the emulsions, to making more standard emulsions available to biomedical teams, and to the definition of standard protocols for biological experimentation, if one is to arrive at meaningful comparisons and establish structure/properties correlations.

4. "Physiology" of the New Blood Substitutes

Blood substitution in a live animal can be envisioned as being, at the same time, an artificial organ transplant and a multi-organ perfusion. It is therefore essential to investigate the tolerability of the emulsions, their interactions with the animal's natural blood components, and more generally their cytotoxicity and effect on the organs and principal functions of the organism. Various but generally unrelated studies have been undertaken in this connection. Unfortunately, they often suffer from poor choice of the perfluoro compound or emulsifying conditions and from a lack of precise definition of the perfusing media. Moreover, no two investigators used the same procedures for the preparation, administration, and testing of the emulsions, which frequently led them to contradictory interpretations, and this often makes it illusory to draw definite conclusions at the present time. The amount of perfluoro compounds present in the organs and body fluids is most efficiently determined by gas chromatography[46, 116, 117] or pycnometry[91].

[*] Failures, leading to the death of the animals transfused, have been observed with these emulsions, and have been traced to hemoconcentration due to an extravasation (or escape) of water from the vascular system which causes the concentration of the perfluorochemicals to rise from 20 to 60%, with subsequent increase in viscosity [85]. *Geyer* also pointed out that some adjustments to the electrolyte composition had to be made to permit their successful use [93]. This again illustrates the importance of achieving adequate fluid balance.

4.1. Acute Toxicity

It now seems clearly established that, when the ingredients are meticulously purified, any direct toxicity of their emulsions arises not from chemical poisoning, but from a failure to comply with certain limits pertaining to their physical characteristics. For example, the particle size may be too coarse or the vapor pressure too high, leading to gaseous embolism (as is the case for FX-80)[110] and lung edema, or inadequate osmotic pressure.

4.2. Residence Time in the Bloodstream

It is not enough for the emulsion to be non-toxic; the perfluoro compounds should not be withdrawn too rapidly from the bloodstream. It is basically a question of baffling the reticuloendothelial system whose role it is to eliminate foreign particles from the bloodstream, but as yet very little is known about the possible reactions of this system to intruders as unnatural as perfluoro compounds. Their chance of survival may in fact be enhanced by their totally artificial nature: they do not resemble anything recognizable by the organism which therefore puts up only a weak defense.

The length of time the fluoro compounds remain in the bloodstream has been found to depend largely on the size of the particles[24, 40, 47, 52], as illustrated in Figure 6 which

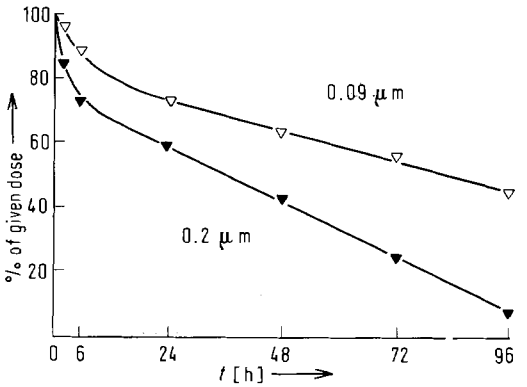


Fig. 6. Comparison of intravascular persistence of FC-43 between fine (average diameter 0.09 µm) and coarse (average diameter 0.2 µm) FC-43 emulsions in rabbits (from ref. [40]).

also shows that half-lives of several days may be obtained with a particle size of less than 0.1 µm. The intravascular persistence of the fluorochemicals was also found to be drastically influenced by the nature of the surfactant[45, 47], but it is not clear whether this is due to some direct action of the surfactant, to its faster elimination, or to differences in particle size.

Small particles appear to have little or no influence on the phagocytic activity of the reticuloendothelial system. Yet, according to some reports, blood appears to have some capacity for modifying the stability of the *F*-decalin and yolk phospholipid emulsions and the size of their particles[56]. This would suggest that the organism possesses some means of agglomerating foreign particles of almost colloidal size until they become phagocytable. On the other hand, particles larger than 1 µm are rapidly eliminated from the bloodstream, and tend to be deposited in the liver. Coarse emulsions may even cause a blockage of the reticuloendothelial system, which

then becomes unable to clear the blood of injected carbon particles[40].

4.3. Retention in the Organs and Excretion

A major physiological problem is raised by the fate of the perfluoro compounds when they have fulfilled their mission. After a period of residence in the bloodstream, whose length closely depends on the size of the particles and on the nature of the surfactant, the perfluoro compounds are removed from the circulation and are in part excreted and in part accumulated in the body. The principal collectors of the perfluoro compounds in the body were found to be the various sorts of mononuclear phagocytes located in the liver and spleen, but also in the bone marrow, lymph nodes, lymphoid tissues, thymus, and so on[27, 28, 43, 47, 72, 73]. To our knowledge there has never been any evidence reported of the perfluoro compounds' being catabolized. The search for fluoride ions in the blood[27], plasma, liver, and femoral bone, using a specific fluoride electrode[43], and for catabolites in the exhalation gases, liver, and spleen by VPC/mass spectrometry[43] gave negative results. When the perfluoro compounds are excreted it is in the original form by exhalation and through the skin[27, 32a], their rate of exhalation being highly dependent on their vapor pressure[40, 49, 55] (Fig. 7). Only trace amounts of perfluoro compounds were occasionally detected in feces, and none in the urine[27, 55].

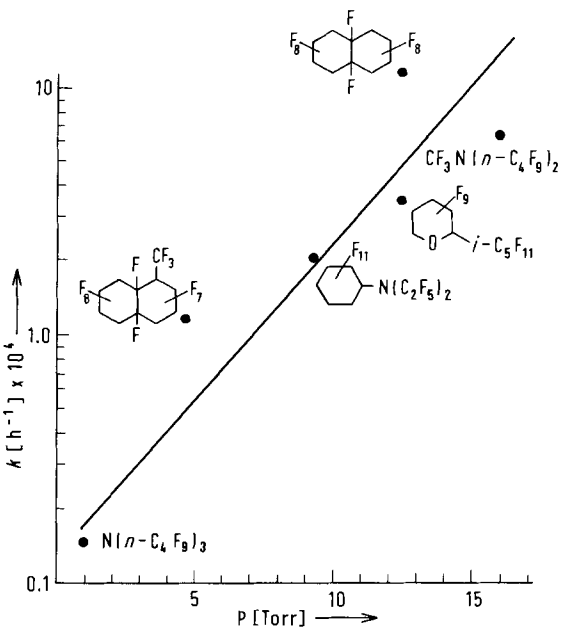


Fig. 7. Relationship between vapor pressure P of perfluoro compounds at 37°C and expiratory excretion rate constant k (from ref. [49]).

The retention time in the organs depends largely on which perfluoro compound is utilized. Some appear to stay there almost indefinitely; this is the case with *F*-tri-*n*-butylamine, while *F*-decalin (which unfortunately gives less stable emulsions) is eliminated in the space of a few weeks[32, 33, 40]. Figure 8 shows that, for the same dose, about 60% goes to the liver for *F*-tributylamine (FC-43), as compared with about 30% for *F*-decalin (FDC), but more important is the fact that after two weeks less than 1% of the *F*-decalin remains present in the liver, while the amount of *F*-tri-*n*-butylamine shows little or no decrease. There is a report according to which the excretion rate of *cis*-*F*-decalin is somewhat greater than that of the *trans* isomer[58]. What causes this retention is not yet clear. An early suggestion according to which the persistence of the compounds in the liver and spleen is linked to the presence of heteroatoms such as oxygen and nitrogen seems to be refuted by the long-term retention observed for *F*-methyldecalin[51], while on the other hand *F*-*N*-methyldibutylamine is eliminated rapidly[55].

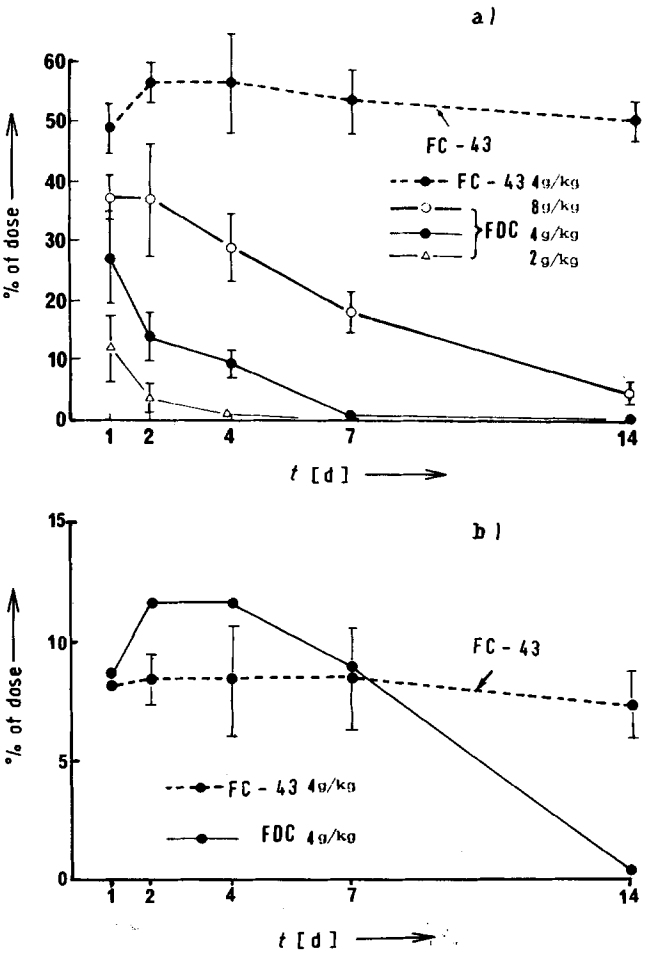


Fig. 8. Comparison of the elimination of *F*-decalin (FDC) and *F*-tri-*n*-butylamine (FC-43) from a) liver and b) spleen (from ref. [40]).

The morphological changes induced by *F*-tri-*n*-butylamine and *F*-decalin in the liver of mice, dogs, and cats were closely monitored microscopically. Only minor alterations, and no tissue toxicity, were observed in the liver, and the parenchyma, endothelium, and phagocytes regained their normal appearance upon elimination of the fluoro compounds[28, 72]. More recent experiments, however, performed with *F*-tri-*n*-butylamine on mice, evidenced some changes in reticulo-histiocytic and hemopoietic cells[73]. During other studies performed on dogs massively infused with *F*-decalin and yolk phospholipid emulsion, no irreversible damage appeared to have been caused to the tissues of the liver, spleen, kidney, lung, bone marrow, testes, endocrine organs, or hemopoietic cells[61].

4.4. Effect of the Emulsions on the Functioning of the Organs

The first organ to be considered is blood itself. It has been shown *in vitro* that a *F*-decalin emulsion and blood

do not influence each other's oxygen dissolution curves[44, 118]. *In vivo* an interaction of the fluoro compound-based substitutes resulting in platelet aggregation has been observed by some authors[51], and was considered responsible for pulmonary failure and death through blockage of the capillaries, while no aggregation or drop in platelet numbers was found by others[4], who see in this a dramatic illustration of how strongly the physiological and biochemical response to an artificial substitute depends upon its preparation. A prior hemodilution has been recommended as a way of circumventing this possible pitfall[61]. Some preparations also caused marked changes in blood clotting patterns[84], while others had no effect on the sedimentation rate of the red cells nor on hemagglutination related to blood grouping[49]. Distentions of blood vessels and of the right ventricle are believed to be a possible result of hemoconcentration[85]. On the other hand, the hemocompatibility of some preparations is clearly indicated by the survival of animals after total blood substitution, by the absence of significant changes in about 20 blood components analysed in a massive blood substitution experiment on monkeys[35], and by the successful use of perfluoro compounds in extracorporeal blood oxygenation[14, 119].

Cerebral micro-circulation has been studied in intact, partially transfused mice (hematocrit reduced from *ca.* 45 to 10—15 vol-%)[63], and it was concluded that the perfluoro compound-charged blood could support cerebral microcirculation and deliver enough oxygen to the brain to sustain electrical activity and to retain some capacity to respond to—and to recover from—brief periods of anoxia, as shown by increases in brain NADH levels during these periods, and the restoration of normal NADH and oxygen levels afterwards. Unfortunately, these studies were performed with "toxic" FX-80 emulsions again, and the author himself considers that it would be advisable to repeat them with a better suited material.

Rat liver, because it has manifold metabolic functions and because it displays an acute sensitivity to oxygen supply, has been extensively used for testing the gas-carrying capacity of perfluoro compound emulsions. The studies performed on live animals were mainly directed at localizing the perfluoro compounds in the organ[27, 28, 50, 72, 73] and the lesions their presence may have caused, while those performed on isolated livers were essentially devoted to the establishment of long-term perfusion systems for isolated organs[65, 74–77].

In a typical study[74] it was shown that a constant hepatic function could be maintained for at least 20 hours with a FC-43/Pluronic F-68 emulsion. Several representative liver functions, including bile production, maintenance of the metabolite steady state, linear release of various enzymes, galactose elimination from the perfusate, induction of tyrosine aminotransferase by dexamethasone, were monitored for a 10—20 hour period, and the results compared with those obtained with a commonly used red-cell-containing medium; and it was concluded that the fluorocarbon emulsion provided at least the same, or an even better hepatic function than the latter medium, with which functional impairment was generally observed after 5—6 hours, probably as a consequence of the aggregation of erythrocytes damaged by the mechanical action of the perfusion apparatus.

Other authors also found that perfusion of the isolated rat liver with FC-43 or FC-80 emulsions maintained the liver in good functional condition for at least 6 hours, as demonstrated by the synthesis of albumin and other proteins, incorporation of ^{14}C-labeled lysine into circulating proteins, secretion of bile, level of alanine aminotransferase, urea, and glucose in the perfusate, vitamin B_{12} binding capacity, fluid pressure in the portal vein, and so on[62, 65, 75–78]. These authors concluded that the perfluoro compounds could supply the organ with oxygen, and that they did not interfere with its functioning provided an optimal flow rate and a high oxygen partial pressure were employed. Indeed, it was found that the effectiveness of the FC-80 emulsion relative to that of other perfusion media depends on the flow rate[62, 75–77, 79]. This may explain some earlier conflicting reports[53, 65, 79].

Some interference with the liver cell metabolism has been recorded in the case of *F-n*-hexane: the fluorocarbon interacts with cytochrome P-450, to the same extent as hexane or cyclohexane, which triggers off NADPH oxidation; but, in contrast to the hydrocarbon substrates, its C—F bonds resist attack by the active oxygen. It therefore behaves as a dead-end inhibitor, which uncouples electron transport from mono-oxygenation[120]. The significance of such an uncoupling process for microsomal monoxygenases is however difficult to assess, since partial uncoupling seems to occur frequently, and was even found for *n*-hexane[120b].

Several attempts at kidney preservation either with pure perfluorochemicals[121] or with their emulsions[80, 81, 122, 123] have been made. Renal functions appeared to be dramatically improved when plasma was replaced by an FX-80 emulsion in the perfusion of the isolated organs[80]. However, despite these good perfusion characteristics, their transplantation after a 24 h period back into the donor animal—which then underwent a contralateral nephrectomy—was less successful than with kidneys perfused with plasma alone. Better results than with plasma alone—better creatinin clearance, and survival of all the five dogs which underwent transplantation[81]—were obtained with FC-43 emulsions.

Perfusion of isolated human ovaries by an FC-47/Pluronic F-68 emulsion was performed in order to evaluate the usefulness of experiments using an artificial medium which allows the experimental parameters to be controlled more closely[82]. It showed that glucose was utilized and lactate produced at a fairly constant rate for as long as 20 hours of perfusion, giving evidence of considerable metabolic activity in the perfused organs. ^{14}C-Progesterone and ^{14}C-17α-hydroxyprogesterone were synthesized from ^{14}C-acetate; estradiol was also secreted, and the production of these steroids appeared to be responsive to gonadotropins.

Hormonal regulation of tyrosine transaminase synthesis was investigated using isolated rat liver perfused with an emulsion containing perfluoro compounds[83]. It revealed remarkable differences from the effects observed when natural perfusion media were used. This exemplifies a new approach to the study of the regulation of organ function.

5. Outlook

5.1. Potential Uses of the New Blood Substitutes[2]

One should consider the artificial blood substitutes, not as a replacement of natural blood, but as a complement,

which permits a wider range of applications both in practice and for research purposes.

As a substitute for whole blood, with functions related to gas transport and maintaining of blood volume and oncotic and osmotic pressure, their use will complement that of natural blood in cases of blood losses accompanying hemorrhage, surgical interventions, and organ perfusion. Since no typing is required, these blood substitutes will be utilizable without delay in case of emergency or disaster. Substantial saving in natural blood will be possible during surgical interventions, and especially when extracorporeal techniques, which require large quantities of blood, are used (in the case of pulmonary failure, for example). They will be particularly suited to organ preservation and the consequent development of organ banks, which at present are severely limited by the brief *in vitro* life of red cells and plasma proteins, due to their vulnerability to the mechanical effects of pumps, oxygenators, and filters, and to the formation of debris which may gradually block the microcirculation of the organs. They will also make "blood transfusion" possible in animal surgery and veterinary medicine, for which no blood banks exist. Among the most serious limitations in these uses of the artificial blood substitutes at present existing, one should however mention the absence of bloodclotting factors and antibody defenses.

Where only the oxygen transport function is considered, the artificial blood substitutes might be useful in the treatment of certain diseases, such as various forms of anemia (aplastic anemia, sickle-cell anemia, cancer-associated anemia), and anaerobic infections, such as tetranus, which respond to the increase of p_{O_2}. In cases of partial blood vessel occlusions, the small size of the perfluoro compound particles should provide a way of circumventing the blood clots, and thus of carrying oxygen to the anoxic sites and at the same time transporting clot-digesting agents to the occluded areas. Total body washout for the removal of viruses, toxins (as in cases of hepatic viral coma), or drug overdoses should find a wide range of applications.

Another domain which will be opened concerns all the uses and experiments in which the presence of the natural blood constituents may mask or modify the action of the materials to be tested. In chemotherapy it could permit the administration of drugs—tumor antibodies for example—that otherwise would react with blood constituents or be attacked by enzymes normally found in the circulation, and therefore fail to reach the target cells.

Bloodless animals will constitute a powerful new tool in biomedical research, since it will become possible to remove and monitor the presence of the various blood constituents. hormones, enzymes, and so on. Thus, for example, investigations into hematopoesis and plasma protein metabolism, hormone production and transport, and detection of as yet unrecognized factors will be possible under precisely controlled conditions. Similarly the effects of various factors on hormone regulation of isolated organs could be studied one by one in clear-cut conditions. The absence of the osmolarity-sensitive red cells could permit action on the blood-brain barrier. The circulatory physiology and hemodynamics could be studied under entirely new conditions, since the viscosity, oncotic and osmotic pressures, and flow characteristics of the circulating fluid could be varied within wide limits, and the effect of the various kinds of blood cells on circulation could be studied separately.

5.2. Obstacles Remaining to be Overcome; Where the Chemist Comes in

Although this research has progressed rapidly, several obstacles remain to be overcome, most of them simultaneously, in order to bring a safe blood substitute into medical practice; and the chemist certainly has a decisive role to play in this connection:

1) It is clear, first, that this research is highly dependent on the availability of the appropriate perfluoro compounds. The chemist has to devise specific routes to numerous (cheap), well-defined, pure, inert perfluoro compounds, perhaps including labeled compounds. These compounds have to form homologous series, in order to permit the step-by-step adjustment of the most crucial parameters and the determination of which compounds and surfactants are best suited for this use. At present only about two dozen compounds have been tested to any extent (Table 2), and the only repeated achievement of *total* blood substitution with subsequent survival so far seems to have been that with *F*-tri-*n*-butylamine. On the other hand, massive substitutions have been successfully performed with *F*-decalin. The hitherto extensively used FX-80 has to be eliminated from the race as being too volatile and therefore definitely toxic. None of the other commercially available perfluorinated ethers (P-1D, P-11D, Freon E) has found acceptance. Encouraging preliminary results have been obtained with bis-*F*-alkylethenes; these substances give more stable emulsions than *F*-decalin, permit survival of rats after total blood substitution, and exhibit higher excretion rates than *F*-tri-*n*-butylamine[124].

2) The *in vivo* stability of the emulsions is a requirement of paramount importance. Thus it may be that *F*-decalin will have to be abandoned, in spite of its remarkable excretion properties, if one does not find a surfactant which confers upon its emulsions a better *in vivo* stability and a longer persistence in the bloodstream than the presently-used yolk phospholipids. The necessity of having precise standard reproducible preparation procedures for the emulsions is now recognized, and many efforts will have to be devoted to making more numerous standardized emulsions available for biomedical experimentation. The chemist may contribute to the engineering, analysis, and characterization of these emulsions, to the preparation and testing of new or modified surfactants, and to the matching of perfluoro compound and surfactant to obtain maximum emulsion stability.

3) Another crucial aspect concerns the optimization of fluid balance and the control of osmolarity. The osmotic and oncotic pressures must be kept very close to normal range, and many research groups appear to stumble at this point. The effects of certain adjuvants on these parameters, as well as on the stability and flow characteristics of the emulsions, certainly require further attention.

4) The long-term retention of some otherwise very attractive fluorochemicals such as *F*-tributylamine is probably the most serious impediment to their use in fluorochemical-based blood substitutes for humans. The origin, extent, and possible long-term effects of this retention clearly deserve further extensive investigation. For all these physiological aspects of blood

substitution, it is essential for the chemist to keep in close contact with the medical corps.

5) The chemists' efforts would have further utility in their contribution to the search for properties *vs.* structure relationships. In this respect, almost everything still remains to be done, and the few hypotheses that have been formulated (increased toxicity when hydrogen atoms are present in the perfluoro compound, increased stability of its emulsions, but also prolonged retention in organs, when it contains nitrogen or oxygen atoms) have not been borne out by further observations.

6) Besides these scientific and medical problems, the introduction of an artificial blood substitute into medical practice will encounter a wide range of further obstacles, including compliance with regulations and acceptance by the physicians and public, as well as various economic, social, and political issues.

In spite of these remaining drawbacks, the perfluoro compound-based blood substitutes seem to be the closest solution to the problem of blood replacement, including the oxygen-carrying function normally performed by the erythrocytes, within reach in the near future.

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Phytoalexins, Chemical Defense Substances of Higher Plants?

By Hans Grisebach and Jürgen Ebel[*]

Phytoalexins are defense substances with antimicrobial properties which are produced by plants after infection. They include various groups of natural substances (*e.g.* isoflavonoids, terpenoids, polyacetylenes and dihydrophenanthrenes). Induction of phytoalexin formation can be caused not only by living microorganisms but also by products of microbial origin (elicitors) or by stress treatment (cold, UV light). The elicitor from the mycelial walls of the fungus *Phytophthora megasperma* var. *sojae* (Pms) is a β-1,3-glucan with branches at C-6. In some cases the basic features of the biosynthesis of the phytoalexins are known. The activity of the enzymes involved in phytoalexin biosynthesis is increased by the action of the elicitor on plant tissues. The ability of some microorganisms to chemically modify the phytoalexins may be related to their pathogenicity. The role of phytoalexins as defense substances is not yet fully clear.

1. Introduction

As is the case with humans and animals, plants are also exposed to numerous microorganisms. The phytopathogenic fungi and viruses are especially important pathogenic agents. Since plants do not possess an immune system, the question is raised as to how they can protect themselves against these pathogenic agents. One possibility, which depends on the induced production of chemical defense substances, will be dealt with in this article.

At the end of the 19th century, it had already been assumed that plants could have an acquired resistance and could react against infection by means of biochemical defense mechanisms[42]; it was, however, the studies of *Müller* and *Börger* on the Phytophthora resistance[**] of potatoes[43] which first led to decisive experimental progress in the elucidation of such defense mechanisms. The essential results of these investigations were: 1. Death of the parasite on the tubers of the resistant varieties was not due to a substance which already existed before infection "but is the result of *a change in the state* of the host cells which have come into contact with the fungus". 2. The plants defend themselves against the parasite by sacrificing the tissue layers infected by the fungus. During this reaction which is termed "defense necrosis", a defense substance is formed which was called "phytoalexin" (phyton = plant, alexin = to defend). Phytoalexins can thus be defined as defense substances with antimicrobial properties which are produced post-infectionally[***] by the host[44, 171].

Further investigations led to the important finding that the intensity of the defense reaction depended primarily on the genetic constitution of the host plant and the parasite[95, 170].

In 1960 a compound with fungitoxic properties was isolated by the drop-diffusate technique[*] from seed pods of peas *(Pisum sativum)* which were infected with spores of the fungus *Sclerotinia fructicola*[46]. The compound was called pisatin; its pterocarpan constitution [Table 1 *(17)*] was elucidated in 1962 by *Perrin* and *Bottomley*[45].

In the past few years the field of the phytoalexins has been intensively studied. Only the more recent of the numerous reviews are cited here[2a, 2b, 23, 24, 47].

The present article deals mainly with the biochemical aspects of the phytoalexins, their induction mechanism and biosynthesis being the principal topics. The role of the phytoalexins as defense compounds against infectious agents is also discussed.

2. Structure and Distribution of Phytoalexins

Phytoalexins are not a uniform class of substances but include various groups of natural products. The phytoalexins so far known are compiled in Table 1. The only compounds considered were those which satisfied the criteria of the phytoalexin concept, (*i.e.* substances which only appear in high concentrations after infection and which inhibit the growth of microorganisms). As can be seen from Table 1, the phytoalexins include isoflavonoids, sesquiterpenes, furanoterpenoids, polyacetylenes, dihydrophenanthrenes and other substances. A comprehensive survey of the nature and distribution of postinfectional defense substances in plants does not yet exist but there is a relationship between the chemical nature of the phytoalexins and the plant families[10]. The legumes generally produce isoflavonoids, the solanaceae diterpenes, the compositae polyacetylenes, and the orchidaceae dihydrophenanthrenes. Exceptions such as the formation of the furanoacetylene, wyeronic acid *(33)*, in broad beans *(Vicia faba)* are rare. In some cases phytoalexins can thus be used as taxonomic markers.

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[**] The fungus *Phytophthora infestans* (Phytiaciae) causes potato rot ("late blight"). It was the reason for the destruction of the Irish potato crop in 1845 and the years following, and resulted in extensive famine.

[***] There are also preinfectional defense substances. This group includes fungitoxic compounds which are already present in sufficient concentrations in non-infected plants to prevent infection [2b]. It is difficult to classify some compounds unequivocally as pre- or postinfectional defense substances.

[*] In the drop-diffusate technique a spore suspension of the fungus is introduced as a drop to the tissue in question (here the endocarp (nutrient tissue) of the seed pods). After the defense reaction has been triggered, some of the phytoalexin formed diffuses into the drop and can be extracted from the combined drops with organic solvents.

It is usually difficult to obtain large quantities of phytoalexins from infected plant tissue. In many cases, however, large quantities (30–100 mg) of these substances can be obtained in a relatively simple way by the method of *Keen*[77]. The seeds are cut and incubated for 3 to 5 days in the presence of the microflora found in the untreated seeds. The phytoalexins which are produced can be extracted with organic solvents and then be isolated by common purification procedures (*e.g.* preparative layer chromatography).

3. Induction of Phytoalexin Formation

A large number of studies on host-parasite interactions have shown that the ability to form phytoalexins is widespread in plants. Tissues from all parts of plants can produce phytoalexins in response to infection by pathogenic and non-pathogenic microorganisms. Fungi are exceptionally effective organisms in this respect. As a result of infection of soybeans *(Glycine max)* with *Phytophthora megasperma* var. *sojae*, glyceolin *(20)* can accumulate within 24–48 h from a concentration which is below the detection limit to quantities which account for more than 10% of the dry weight of the infected tissue[187]. Most plants seem to produce several, often structurally related phytoalexins as is clearly the case with green beans *(Phaseolus vulgaris)* and potatoes *(Solanum tuberosum)* (Table 1).

Phytoalexin formation is also found to be induced by infection of plant tissues with bacteria[89,90a–c,146,188,189], viruses[83,91,92,138,139] and nematodes[15,93]. The production of phytoalexins is induced ("elicited") not only by living microorganisms but also by cell-free culture filtrates or extracts[94–102]. Compounds of microbial origin which stimulate phytoalexin synthesis in plants have been named elicitors[103]. The possible biological significance of the elicitors of phytoalexin synthesis in the defense reactions of plants against microorganisms is discussed in Section 5.

Phytoalexins have repeatedly been described as "stress compounds" (*e.g.* [90a]) as their synthesis can, like numerous other primary and secondary metabolites, also be stimulated by different types of treatment which damage or poison plant tissues. Exposure to cold[104] or UV light[105,106] can trigger phytoalexin synthesis. Substances as chemically different as heavy metal salts[94,100,107,108], polyamines[109], ethylene[110], antibiotics and metabolic inhibitors[108,111–115], fungicides[116,117] and ribonuclease[96] are also inducers. These substances probably act in different ways; in every case, however, the result is a profound change in the metabolism of the challenged plant. Phytoalexins have acquired special importance among the compounds produced under stress conditions because, on account of their postinfectional formation and antimicrobial properties, they are associated with the defense reactions of plants against potential pests (see Section 5). If plants produce several phytoalexins, the composition of the phytoalexin mixture may depend on the inducing agent. Examples of this have been mentioned by *VanEtten* and *Pueppke* ([2a], Table IV) for combinations of *P. vulgaris* with four pathogenic microorganisms. *Keen*[177] has proposed a hypothesis based on a similar behavior of *Glycine max*[177], *Phaseolus lunatus*[15] and *Glycine wightii*[78] which states that, as a response to infection with a microorganism, plants preferentially accumulate those phytoalexins which exhibit the strongest inhibitory action against this organism. The response to an abiotic elicitor such as $CuCl_2$ is, on the other hand, less selective.

It is an attractive hypothesis that plants recognize products of microbial origin and that this then brings about induction of phytoalexin synthesis[118]. The first reports concerning elicitors synthesized by microorganisms were based on studies with preparations of unknown composition[94–102]. *Cruickshank* and *Perrin*[119] isolated and characterized an elicitor from *Monilinia fructicola*, a fruit parasite. This elicitor, monilicolin A, is a peptide with a molecular weight of approximately 8000 which, when applied in low concentrations (*ca.* 10^{-9} mol/l) stimulates the synthesis of the phytoalexins phaseolin *(18)* and phaseolidin *(19)* in beans *(Phaseolus vulgaris)*[119]. Beans, however, are not a host plant for this fungus. Monilicolin A does not stimulate phytoalexin synthesis in other non-hosts of this fungus such as the broad bean *(Vicia faba)* or pea *(Pisum sativum)*[119]. The physiological significance of monilicolin A in disease resistance is still not clear since a host of *M. fructicola* which reacts towards this elicitor has not yet been described.

Albersheim et al.[118,120–123] isolated an elicitor from *Phytophthora megasperma* var. *sojae* (abbreviated as Pms), the cause of stem and root rot in soybeans *(Glycine max)*. The Pms elicitor induced the synthesis of glyceolin *(20)* in cotyledons[120], hypocotyls[120] and cell suspension cultures[123] of soybean[*]. The various tissues of soybean react very sensitively to small quantities of the Pms elicitor. Concentrations of approximately 1 μg/ml are sufficient to stimulate glyceolin accumulation. No distinction was made between *(20)* and the structurally isomeric compounds *(21)* and *(22)* which were isolated by *Lyne et al.*[14] from infected soybeans and which had antimicrobial properties similar to those of glyceolin; this is because these compounds were not determined separately under the conditions used for the biological assay of the Pms elicitor.

The Pms elicitor is a structural polysaccharide of the mycelial walls of Pms. It can be partially solubilized from the walls with water on heating. The elicitor can also be isolated from cell-free culture filtrates of Pms and is presumably released into it by autolysis of the fungal mycelia. The stability of the Pms elicitor to heat for several hours, its insensitivity towards pH extremes, its resistance to pronase and the heterogeneity of its molecular weight indicated that it was a polysaccharide[118].

A more detailed characterization showed that the elicitor-active molecules were β-1,3-glucans which can have additional sugar residues at C-6 of some of their glucosyl residues. The average molecular weight of the elicitor extracted from the mycelial walls is 100000. Exo-β-1,3-glucanase from *Euglena gracilis* hydrolyzes approximately 90% of the glucan to give highly branched fragments with an average molecular weight of approximately 10000. These fragments contain most of the elicitor activity of the high molecular weight material. In order to characterize the elicitor-active glucan components even more accurately, the Pms mycelial walls were partially hydrolyzed with acid. Oligosaccharides containing approxi-

[*] The cotyledons (seed leaves) and the hypocotyl (section of the shoot between the origin of the root and the cotyledons) are parts of the seedling.

Table 1. Structure and distribution of the phytoalexins (further references are given in review articles [2a, 2b, 23, 24]).

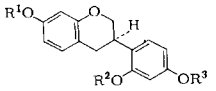
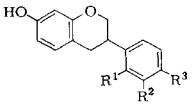
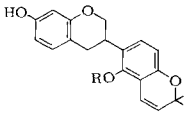
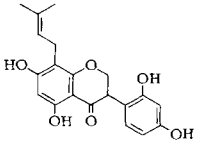
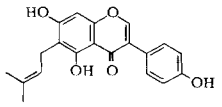
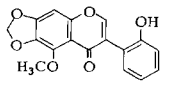
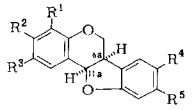
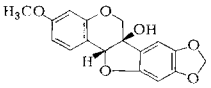
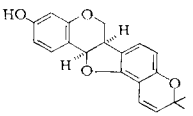
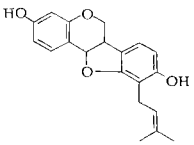
Structure	Trivial name	Source
Isoflavonoids		
(1), $R^1=R^2=CH_3$; $R^3=H$	Arvesan [1]	Rabbit-foot clover *(Trifolium arvense)*
(2), $R^1=H$; $R^2=R^3=CH_3$	Sativan [81]	*(2)*, *(4)*, *(5)* also in other varieties of clover
 *(3)*, $R^1=CH_3$; $R^2=H$; $R^3=CH_3$	Isosativan [31]	Alsike clover *(Trifolium hybridum)* and other varieties of clover
(4), $R^1=R^2=H$; $R^3=CH_3$	Vestitol [10, 81]	*(2)* and *(4)* also in *Trigonella* and sain foin *(Onobrychis viciaefolia)* [178]
(5), $R^1=R^3=H$; $R^2=CH_3$	Isovestitol [3]	also in lotus species, Hyacinth bean *(Lablab niger)* [177]
(6), $R^1=R^2=R^3=H$	Demethylvestitol [3]	*Tetragonobulus* species
 *(7)*, $R^1=OH$; $R^2=R^3=OCH_3$	Isomucronulatol [4]	*Glycyrrhiza* (licorice) species
(7a), $R^1=R^2=OCH_3$; $R^3=OH$	Laxifloran [177]	Hyacinth bean
(8), $R^1=OCH_3$; $R^2=$ Dimethylallyl; $R^3=OH$	2-*O*'-Methylphaseolidin-isoflavan [32]	Cowpea *(Vigna unguiculata)*
 *(9)*, $R=H$	Phaseolinisoflavan [5]	Bush bean *(Phaseolus vulgaris)*
(9a), $R=CH_3$	2'-*O*-Methyl derivative of *(9)* [82]	
 *(10)*	Kievitone [5]	Bush bean, hyacinth bean [177]
 *(10a)*	Wighteone [78]	*Glycine wightii*
 *(11)*	Betavulgarin [6, 7]	Beet *(Beta vulgaris*, Chenopodiaceae)
 *(12)*, $R^1=R^3=R^4=H$; $R^2=OH$; $R^5=OCH_3$	Medicarpin [8], [(−)-enantiomer, (6a*R*,11a*R*)-configuration]	Common clover *(Trifolium pratense)*, Lucerne *(Medicago satifa)*, *Canavalia ensiformis*, Stone (sweet) clover *(Melilotus)* [9] and *Trigonella* species [10], sain foin *(Onobrychis viciaefolia)* [178]
(13), $R^1=R^4=H$; $R^2=OH$; $R^3=R^5=OCH_3$ *(14)*, $R^1=R^4=H$; $R^2=R^3=R^5=OCH_3$ *(15)*, $R^1=OH$; $R^4=H$; $R^2=R^3=R^5=OCH_3$ *(16)*, $R^1=R^3=H$; $R^4-R^5=-O-CH_2-O-$	(−)-Inermin [8] (Maackiain)	Together with *(13)*—*(15)* and *(17)* from peas. *(16)* also from *Trigonella* species [10]
 *(17)*	(+)-Pisatin [a] [45]	Peas *(Pisum sativum)*, Flat pea *(Lathyrus)* [11]
 *(18)*	Phaseolin [33] [(6a*R*,11a*R*)-configuration] [34]	*Phaseolus* species, common cowpea *(Vigna sinensis)*
 *(19)*	Phaseolidin [5, 12]	*Phaseolus vulgaris*, *Vigna sinensis* [83], goa bean *(Psophocarpus tetragonolobus)* [84], hyacinth bean [177]

Table 1. (cont'd)

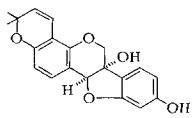
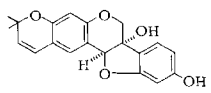
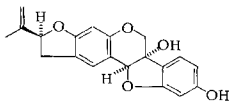
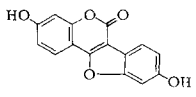
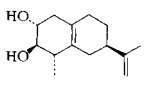
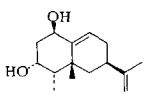
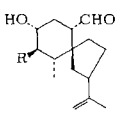
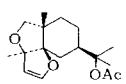
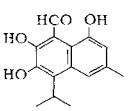
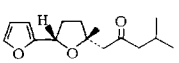
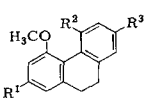
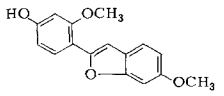
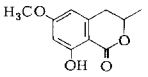
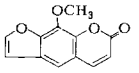
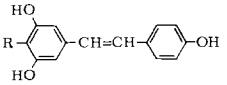
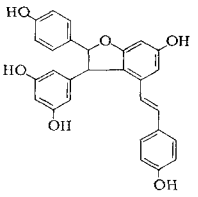
Structure		Trivial name	Source
	*(20)*	Glyceolin [13]	Soybean *(Glycine max)*
	*(21)*	Isomer of Glyceolin [14]	Soybean
	*(22)*	Isomer of Glyceolin [14]	Soybean
	*(23)*	Coumestrol [b] [15]	Sieva (lima) bean *(Phaseolus lunatus)*
Sesquiterpenes (for a review see also [90a]*)*			
	*(24)*	Rishitin [35, 36]	Potatoes (*Solanum*-Arten), tomatoes *(Lycopersicum esculentum)*
	*(25)*	Capsidiol [22, 37]	Paprika fruit *(Capsicum frutescens)*
	*(26)*, R = H *(27)*, R = OH	Lubimin [38] 4-Hydroxylubimin [c] [39]	Potatoes, jimson weed *(Datura stramonium)*
	*(28)*	Phytuberin [40]	Potatoes
	*(29)*	Hemigossypol [41, 19]	Cotton (*Gossypium* species, Malvaceae)
Furanoterpenoids			
	*(30)*	Ipomeamarone [25]	Sweet potato (*Ipomoea batatas*, Convolvulaceae)
Polyacetylenes			
$CH_3-CH=^{t}CH-(C\equiv C)_3-CH=^{t}CH-CH(OH)-CH_2OH$	*(31)*	Safinol [26, 85] [(2*R*)-configuration]	Safflower (*Carthamus tinctorius*, Compositae)
$CH_3-CH=^{t}CH-(C\equiv C)_4-CH(OH)-CH_2OH$	*(32)*	Dehydrosafinol [26]	
$C_2H_5-CH=^{c}CH-C\equiv C-C(=O)-$ 	*(33)*, R = H *(34)*, R = CH_3	Wyeronic acid [27, 28] Wyerone	Broad bean *(Vicia faba)*
$C_2H_5-CH(O)-CH-C\equiv CH-C(=O)-$ 	*(35)*	Wyerone-4,5-epoxide [29]	
Dihydrophenanthrenes			
	*(36)*, $R^1 = OCH_3$; $R^2 = H$; $R^3 = OH$ *(37)*, $R^1 = R^2 = OH$; $R^3 = H$ *(38)*, $R^1 = OCH_3$; $R^2 = OH$; $R^3 = H$	Orchinol [20, 21] Hircinol Loroglossol [30]	Orchid tubers (Orchidaceae)

Table 1. (cont'd)

	Structure	Trivial name	Source
Miscellaneous			
	*(39)*	Vignafuran [d] [16]	Cowpea *(Vigna unguiculata)*
	*(40)*	[17]	Carrots *(Daucus carota)*
	*(41)*	Xanthotoxin [18]	Parsnip *(Pastinaca sativa)*
	*cis-* and *trans-(42)*, R = H	Resveratrol [86]	African ground nut *(Arachis hypogea)*
	cis- and *trans-(43)*, R = Dimethylallyl	[87]	American ground nut
	*(44)*	ε-Viniferin [e] [88]	Grape *(Vitis vinifera)*

[a] Since pisatin *(17)* as opposed to most natural pterocarpanes is dextrorotatory, it is assumed to have a (6a*S*,11a*S*)-configuration.
[b] Coumestrol *(23)* is accumulated after infection with the nematode *Pratylenchus scribneri*. It inhibits the mobility of this nematode but does not have a fungitoxic action.
[c] The fungitoxicity of *(27)* seems to be lower than that cited by *Katsui et al.* [39, 90a].
[d] Vignafuran *(39)* could be formed from a pterocarpene [cf. *(12)*].
[e] Resveratrol *(42)* which is also found in the grapevine may be the precursor of ε-viniferin *(44)*. *(44)* is significantly more fungitoxic than *(42)* [88].

mately eight glucosyl residues were isolated from the hydrolysate and were the smallest elicitor-active compounds[118].

Periodate oxidation of the elicitor preparation results in almost complete loss of activity in its biological assay[122]. A considerable part of the elicitor activity is, however, regained on reduction with $NaBH_4$ and subsequent acid hydrolysis under mild conditions. This finding suggests that periodate destroys the elicitor activity by modifying terminal glycosyl residues. Partial acid hydrolysis leads to liberation of new terminal glycosyl residues and thus to reactivation[118].

Elicitors with similar biological activities have been isolated from three races of Pms which differ in their pathogenicity towards soybean[121, 122]. Figure 1 shows the rate and extent of glyceolin accumulation in hypocotyls of soybean which were incubated with living mycelium of either a virulent Pms race, of an avirulent race, or elicitors isolated from these races[121]. In all three cases the glyceolin content of the hypocotyls starts to increase considerably 6—9 hours after the beginning of the incubation. Between 9 and 15 hours the increase continues in the same way in all three cases. The finding that the purified Pms elicitor induces glyceolin synthesis to the same extent as the Pms mycelium suggests that the elicitor is the component of the mycelium which is recognized by the plant[118]. The Pms elicitor should thus be an excellent agent in a model system for studying phytoalexin synthesis in soybean.

The biosynthesis of glyceolin *(20)* probably proceeds *via* the central intermediate of flavonoid biosynthesis, the flavanone (cf. Fig. 2 and Section 4). Induction experiments with elicitors in cell cultures[123] and cotyledons[64a, 64b] of the soybean demonstrated that glyceolin production was accompanied by a large increase in the activities of the enzymes of general phenylpropanoid metabolism (phenylalanine ammonia-lyase (PAL), cinnamic acid-4-hydroxylase, 4-coumarate: CoA ligase)

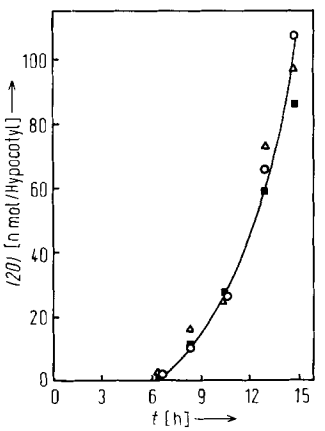


Fig. 1. Accumulation of glyceolin *(20)* after treatment of soybean hypocotyls with the Pms elicitor or with living Pms mycelium. ■, Pms elicitor; ○, mycelium of an avirulent Pms race; △, mycelium of a virulent Pms race (can kill the plant within 24 h).

and flavanone synthase (FS) (Fig. 2). An increase in PAL activity was also observed in other host-parasite interactions[59, 69, 124–129] as well as in mechanically damaged plant tissues in which the synthesis of phenylpropanoid compounds and the activity of the enzymes involved in general phenylpropanoid metabolism are stimulated[124, 130–133]. These observations leave doubt as to whether the increases in PAL activity measured in the host-parasite systems were not entirely or partially due to mechanical damage of the plant tissue[190].

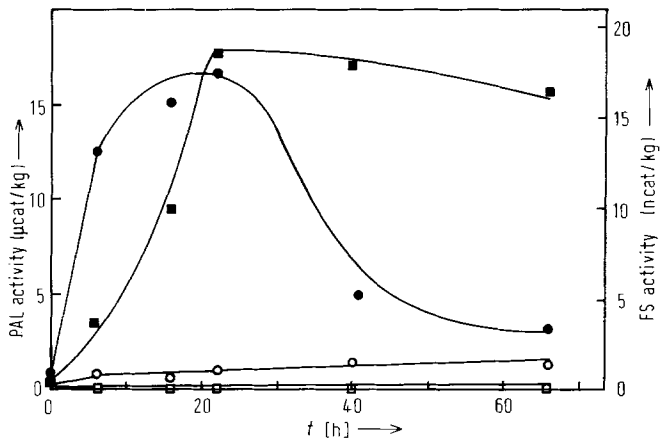


Fig. 2. Time dependence of the elicitor-induced changes in the activities of phenylalanine ammonia-lyase (PAL, ●) and flavanone synthase (FS, ■) in wounded soybean cotyledons. (Open symbols: control experiment with wounded cotyledons without elicitor.)

Induction experiments with mechanically damaged soybean cotyledons showed, however, that the activity of PAL and FS only drastically increased in the damaged cotyledons which were also treated with the Pms elicitor (Fig. 2). Induction experiments with soybean cell cultures in which the elicitor was added to the culture medium, also demonstrated increases in PAL activity and glyceolin accumulation which were independent of mechanical damage[123].

One important question concerning control of phytoalexin production is whether the elicitor-induced synthesis of glyceolin in soybean cotyledons is connected with the measured increase in enzyme activities. Incubation of soybean cotyledons with the elicitor and a competitive inhibitor of PAL (a derivative of α-aminooxy-β-phenylpropionic acid[184]) reduces glyceolin accumulation by approximately 60% whereas the *in vitro* activities of the enzymes involved in general phenylpropanoid metabolism correspond with those of the samples without the inhibitor[64b]. This suggests that elicitor-stimulated glyceolin synthesis is at least partially controlled by the enhanced activities of the enzymes of general phenylpropanoid metabolism.

Polysaccharide elicitors and their effects on phytoalexin synthesis are not restricted to the Pms/soybean system. Glucans similar to those from Pms are found in the walls of a large number of fungi[185]. Glucans from yeast (*Saccharomyces cerevisiae*)[118], the mycelial walls of *Colletotrichum lindemuthianum*[134] and *Phytophthora* spp.[135] stimulate phytoalexin synthesis in soybean, bean and potato. The molecular processes responsible for the effects of the Pms elicitor and the increased activities of the enzymes involved in phenylpropanoid metabolism are still unknown. It is remarkable that the Pms elicitor also enhances PAL activity in cell cultures of sycamore (*Acer pseudoplatanus*) and parsley (*Petroselinum hortense*)[123].

After virus infection, tobacco (*Nicotiana* spp.) produces a series of substituted cinnamic acids and benzoic acids together with their esters and also coumarins[136, 137] and sesquiterpenes[138, 139]. More detailed information about the antimicrobial properties of the cinnamic acid derivatives and coumarins and their significance as phytoaalexins in this host-parasite system is lacking. In spite of this, some more recent studies on the increase in phenylpropanoid metabolism observed after virus infection will be mentioned. A large increase in the activities of PAL, cinnamic acid-4-hydroxylase and *O*-methyltransferase was observed in virus-infected leaves which formed local necrotic lesions[140–142]. In this case the increased enzyme activity of PAL is due to an enhancement of the rate of enzyme synthesis caused by virus infection[125]. *Tanaka* and *Uritani*[132] came to a similar conclusion when accounting for the increase in PAL activity observed after mechanical damage to roots of the sweet potato (*Ipomoea batatas*).

4. Biosynthesis and Metabolism of Phytoalexins

4.1. Isoflavonoids

The majority of the phytoalexins so far known are isoflavonoids. These compounds are in turn a subgroup of the flavonoids whose biosynthesis is dealt with in recent comprehensive reviews[48, 49].

In order to understand the following account, the metabolic pathway leading to the flavonoids will first be briefly described. The coenzyme A esters of 4-hydroxycinnamic acid (4-coumaric acid) and malonic acid are required for the biosynthesis of the flavonoid skeleton. Cinnamic acid itself is produced by elimination of ammonia from L-phenylalanine which is catalyzed by PAL. After hydroxylation to 4-hydroxycinnamic acid it can be activated by a ligase in the presence of ATP and coenzyme A to its CoA ester. The enzyme flavanone synthase (FS)[50] then catalyzes the condensation reaction of 4-coumaroyl CoA with 3 molecules of malonyl CoA to give the flavanone naringenin (*45*) which occupies a central position in flavonoid metabolism (Fig. 3).

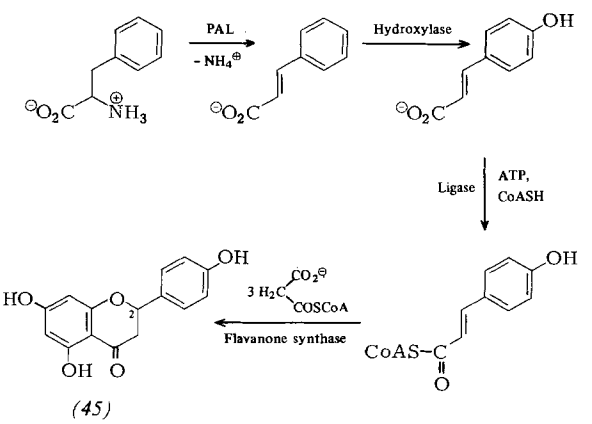


Fig. 3. Biosynthetic pathway from L-phenylalanine to the flavanone naringenin (*45*). PAL = phenylalanine ammonia-lyase.

Isotopically labeled naringenin has been utilized to show that isoflavones, *e.g.* (*46*), with the same type of substitution

as this flavanone[51], are formed by 1,2-aryl rearrangement of (−)-(2*S*)-naringenin. The precursor for the biosynthesis of 5-deoxyisoflavones *e.g. (47)* is 4′,7-dihydroxyflavanone[52] (Fig. 4). As yet, no enzymes are known which can synthesize the dihydroxyflavanone and rearrange flavanones to isoflavones.

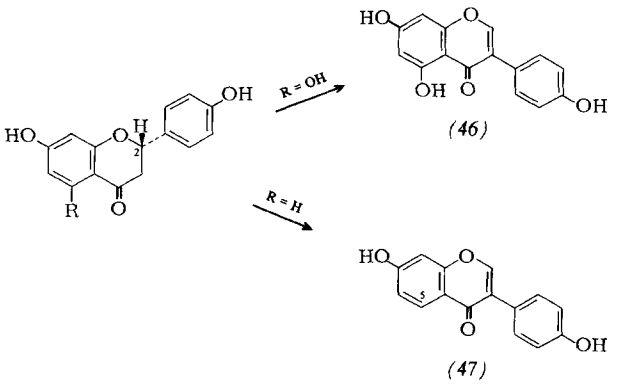


Fig. 4. Biosynthesis of the isoflavone genistein *(46)* and the 5-deoxyisoflavone daidzein *(47)* from the appropriately substituted flavanones.

Details concerning the biosynthesis of the pterocarpan phytoalexins in red clover *(Trifolium pratense)* are known. After fungal infection[53] or in the presence of heavy metal ions (*e.g.* Cu^{2+})[54], synthesis of medicarpin *(12)* and maackiain *(16)* is induced in the seedlings. Incorporation experiments with ^{14}C-labeled precursors showed that 7-hydroxy-4′-methoxyisoflavone (formononetin) *(48)* and the isoflavanones *(49)* and *(50)* were very good precursors for *(12)* but not for vestitol *(4)*. Compounds *(49)* and *(50)* showed higher ^{14}C incorporation than *(48)*[56]. On the basis of these findings the biosynthetic pathway for medicarpin *(12)* shown in Figure 5 has been postulated. According to this, formononetin *(48)* is first hydroxylated to *(49)*. (The 2′-hydroxylation of isoflavanones has been demonstrated in investigations on the biosynthesis of coumestrol *(23)* in *Phaseolus aureus*[55].) The isoflavone *(49)* could be reduced to the isoflavone *(50)* which would, on further reduction, give the isoflavanol *(51)*. Loss of OH^- leads to the carbenium ion *(52)* mesomeric with *(53)* which would be converted into medicarpin *(12)* by cyclization and release of a proton. Vestitol *(4)* could be produced by addition of a hydride ion to the carbenium ion. The existence of the intermediate carbenium ion *(52)* is strongly supported by the mutual interconversion of *(12)* and *(4)* in lucerne *(Medicago sativa)*[57] which apparently takes place *via* a common intermediate. The isoflavene *(54)* could be an alternative to the carbenium ion *(52)*.

The stereochemistry of the reduction sequence from *(49)* to *(12)* was studied with seedlings of *Trigonella foenum-graecum*[*] which accumulate large quantities of medicarpin *(12)* after treatment with $CuCl_2$ or UV irradiation[58]. The medicarpin *(12a)* (Fig. 6) isolated from the seedlings after application of the isoflavone *(49a)* labeled with deuterium at C-2 gave only one signal in its ^2H-nuclear magnetic resonance spectrum at $\delta = 3.92$ which can be attributed to the deuterium in the 6-pro-*R* position. The biosynthesis of *(12)* from *(49)* thus proceeds formally by *trans* addition of hydrogen to the double bond.

The biosynthetic pathway proposed for medicarpin is similar to that for coumestrol *(23)* in seedlings[55] or cell cultures[62] of mung bean *(Phaseolus aureus)*. The pterocarpene *(55)* was postulated to be a direct precursor of *(23)* (Fig. 7) as it can be easily oxidized to coumestrol[63]. In mung bean, however, coumestrol is not a phytoalexin in the strict sense

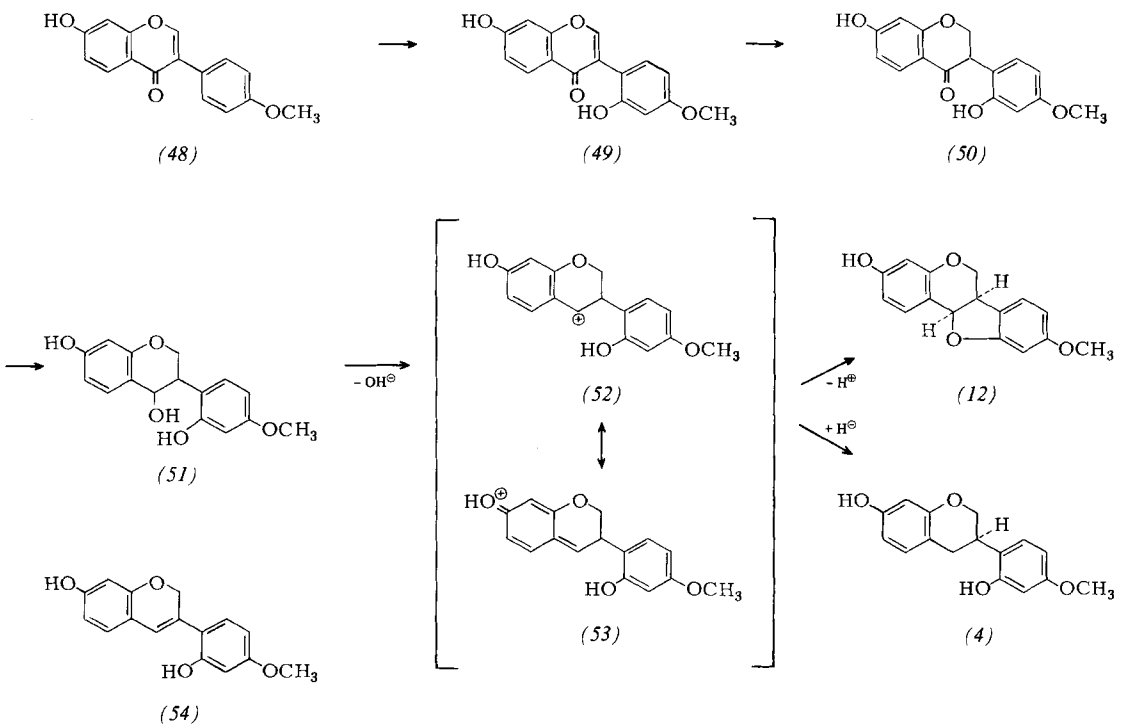
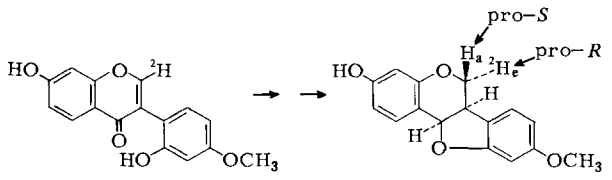


Fig. 5. Postulated biosynthetic pathway from the isoflavone formononetin *(48)* to medicarpin *(12)* and vestitol *(4)*.

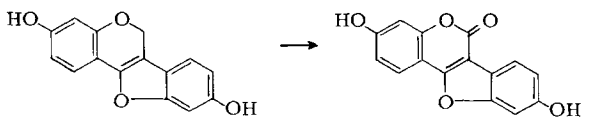
[*] *Trigonella* is the main ingredient of the artificial curry sauce which can be obtained in Germany. It has scarcely anything in common with the asiatic curry mixture.

of the word as it is already present in higher concentrations in healthy tissues.



(49a) (12a)

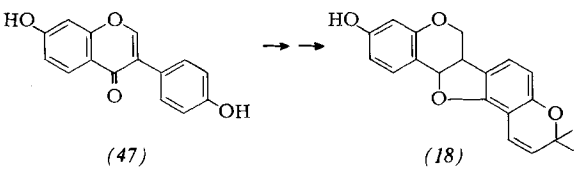
Fig. 6. Stereochemistry of the reduction of 2-deuterioisoflavone (49a) to deuterated medicarpin (12a).



(55) (23)

Fig. 7. Postulated biosynthesis of coumestrol (23) by oxidation of the pterocarpene (55).

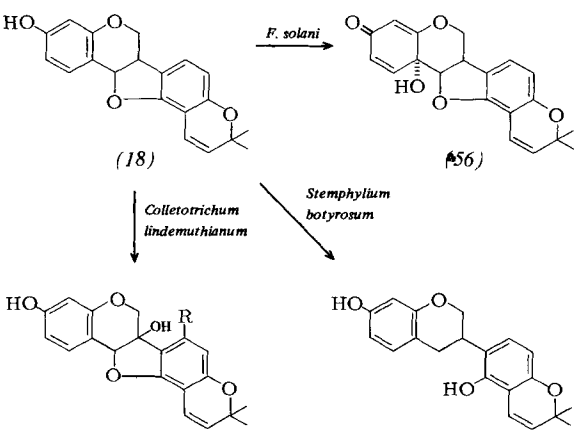
The incorporation of [^{3}H]-daidzein (47) into phaseolin (18) which takes place in bean pods[59] is also similar to the biosynthetic pathway for medicarpin (Fig. 8).



(47) (18)

Fig. 8. Conversion of daidzein (47) into phaseolin (18) (demonstrated by ^{3}H-labeling).

In accordance with the phytoalexin theory, it could be shown in experiments with beans that the precursors of phaseolin (18) only originate from the host plants and not from the parasites. Series of experiments were performed with ^{14}C-labeled spores ([^{14}C]-glucose) of *Sclerotinia fructicola* and with [^{14}C]-glucose-labeled host tissue[60]. The relationship between phytoalexin induction and the increase in the activity of the enzymes which are probably involved in their synthesis has already been discussed in Section 3.



(18) (56)

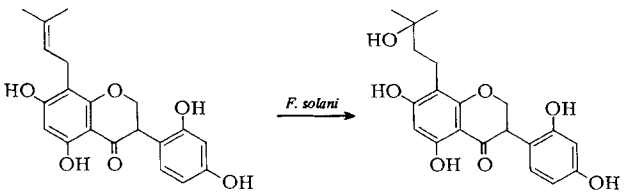
(57), R = H
(58), R = OH (9)

Fig. 9. Conversion of phaseolin (18) by fungi into (9) and (56)—(58).

Phytoalexins can be modified and probably also be catabolized by fungi. These reactions may be a defense reaction of the fungi against the phytoalexins; some of these metabolic products have a lower fungitoxicity (cf. also Section 5). Phaseolin (18) is oxidized to the more weakly fungitoxic hydroxyphaseolin (56) by the fungus *Fusarium solani* which is pathogenic for bean[65, 66] (Fig. 9).

Hydroxylation of (18) to the products (57) and (58)[61] and the reductive opening of the benzyl phenyl ether bond to give phaseolin isoflavane (9) (Fig. 9) are other reactions which are carried out by phytopathogenic fungi (for literature concerning these reactions see [2a] and [2b]). The modified products shown in Figure 9 can very probably be catabolized by the fungi to simple substances; the details of these processes, however, still have to be elucidated.

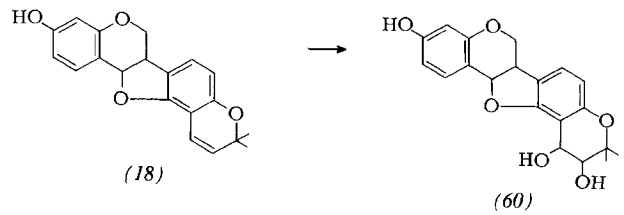
More metabolic products of the pterocarpanes are known[2a, b]. It has recently been demonstrated that kievitone (10) is converted into the product (59) by *Fusarium solani* which formally corresponds to addition of water (Fig. 10)[67].



(10) (59)

Fig. 10. Hydroxylation of kievitone (10) to (59) by *Fusarium solani*.

The metabolism of phytoalexins is not limited to the phytopathogenic fungi. *Septoria nodorum* and other fungi which are not pathogenic towards bean plants can convert phaseolin (18) into the much less toxic *cis*- and *trans*-12,13-dihydrodihydroxyphaseolin (60) (Fig. 11)[68]. Accordingly, the distinction between pathogenic and non-pathogenic fungi, in these cases at least, is not connected with their ability to catabolize phytoalexins.



(18) (60)

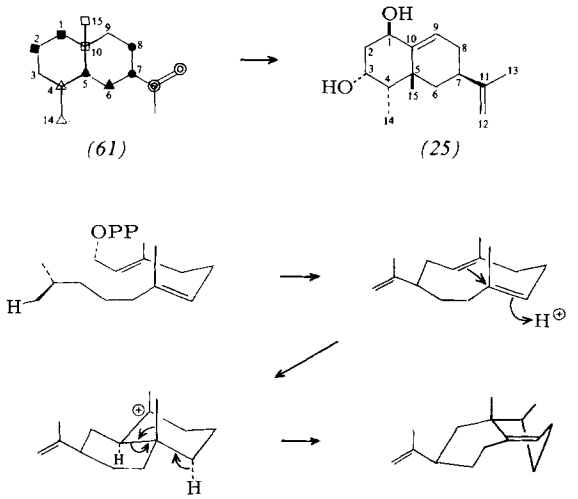
Fig. 11. Hydroxylation of phaseolin (18) to (60) by *Fusarium solani*.

4.2. Sesquiterpenes, Furanoterpenoids

In this section only those experiments will be discussed in which the special features of the biosynthesis of these compounds are recorded, the evidence concerning their origin in general isoprenoid metabolism will not be dealt with[20, 23].

The biosynthesis of capsidiol (25) has been studied by injecting labeled precursors into peppers (*Capiscum annuum*) which had been treated with spore suspensions of *Monilinia fructicola*[70]. After addition of [1,2-$^{13}C_2$]-acetate, ^{13}C-^{13}C coupling between C-1/C-2; C-4/C-14; C-5/C-6; C-7/C-8 and C-11/C-12 could be observed in the ^{13}C-NMR spectrum of (25). In contrast, there was no coupling between C-5 and

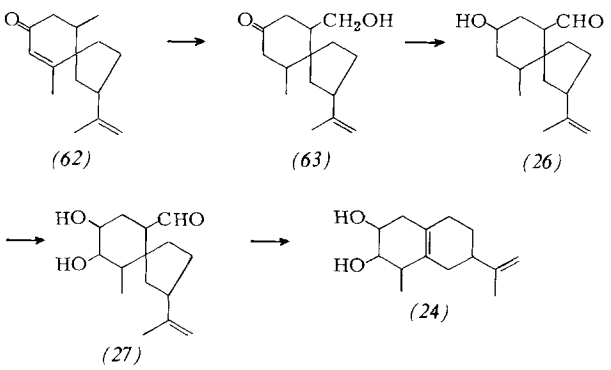
C-15 which proved that these two C atoms do not originate from the same C_2 unit. This finding is in agreement with the hypothesis that the eremophilane skeleton of *(25)* is formed from the eudesmane skeleton *(61)* by migration of a methyl group from C-10 to C-5 (Fig. 12). The reaction pathway postulated for the conversion of farnesyl pyrophosphate into eremophilenes is shown in the lower part of Figure 12.



(61) *(25)*

Fig. 12. Biosynthesis of capsidiol *(25)* from the eudesmane skeleton *(61)* by methyl migration from C-10 to C-5. Lower part: postulated course of the reaction.

Several reports on the biosynthesis of rishitin *(24)* in potatoes have appeared[2b, 23, 71–73]; the biosynthetic pathway shown in Figure 13 was postulated on the basis of these results. The vetispira compounds isolubimin, lubimin *(26)* and 4-hydroxylubimin *(27)* have been proposed as intermediates and are also found to occur as phytoalexins in infected potatoes (Table 1).



(62) *(63)* *(26)* *(27)* *(24)*

Fig. 13. Postulated biosynthesis of rishitin *(24)* from the spirovetivadienone *(62)*. On conversion of 4-hydroxylubimin *(27)* into *(24)*, C-15 (—CHO) is lost [72].

On comparison of the incorporation of ^{14}C-labeled acetate and mevalonate into rishitin *(24)* an up to 5.9-fold higher incorporation was found in resistant potato varieties than in susceptible varieties[73].

The changes in the activities of enzymes which are involved in the biosynthesis of isopentenyl pyrophosphate were investigated after infection of root tissue of sweet potato *(Ipomoea batatas)* by spores of the fungus *Ceratocystis fimbriata*. Figure 14 shows the increase in activity of 3-hydroxy-3-methylglutaryl-coenzyme-A reductase (HMG-CoA reductase) after infection. This increase is followed by an increase in furanoterpenoids such as ipomeamarone *(30)*[74]. In tissue which is only damaged but not infected, however, neither the enzyme activity nor the furanoterpenoid content increases. The conditions are thus very similar to those during induction of glyceolin formation in soybean cotyledons (see Fig. 2).

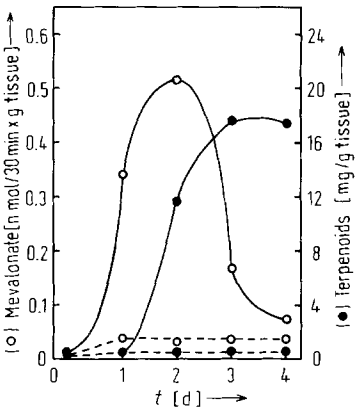
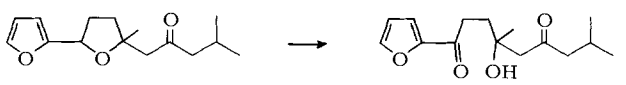


Fig. 14. Changes in the activity of HMG-CoA reductase (○—○) and terpene content (●—●) after infection of the root tissue of sweet potato by spores of the fungus *Ceratocystis fimbriata*. (Dashed curves: control experiment with wounded non-infected tissue).

It is not known whether HMG-CoA reductase is the rate-determining enzyme in furanoterpenoid synthesis as is the case in the biosynthesis of cholesterol in rat liver[75]. Increases in the activity of other enzymes of the pathway from mevalonate to isopentenylpyrophosphate (*e.g.* pyrophosphomevalonate decarboxylase) have been observed after infection of sweet potato[76].



(30) *(64)*

Fig. 15. Oxidation of ipomearmarone *(30)* to 4-hydroxymyoparone *(64)* by sweet potatoes.

Ipomeamarone *(30)* is oxidized to 4-hydroxymyoparone *(64)* by sweet potato slices treated with $HgCl_2$ (Fig. 15)[79]. *(64)* can be converted into lung-toxic metabolites by the fungus *Fusarium solani* which is pathogenic for sweet potato[80].

5. Role of Phytoalexins as Defense Substances

Numerous recent reports have been concerned with the significance of phytoalexins in the resistance of plants against diseases[2a, 23, 24, 47, 90a, 143, 144]. In this article only a few important observations and hypotheses will be dealt with.

Phytoalexins, often several compounds with similar structures, are not only produced as a response of a plant to infection but also, for example, on exposure of the plant to cold or UV radiation; they are also not specific toxins. Specificity is based on the way in which the plants react (susceptibility or resistance) in certain host-parasite combinations[*].

[*] The combination or interaction between the host plant and the pathogenic organism is termed as "compatible" if the host is susceptible and the pathogenic organism is virulent. The combination in which the host is resistant and the pathogenic organism is avirulent is accordingly described as "incompatible" [95].

Before the role of phytoalexins as defense substances can be evaluated, the following questions must be answered:

a) Are phytoalexins produced in sufficient quantities and at the appropiate time to account for the observed cessation of parasite growth?

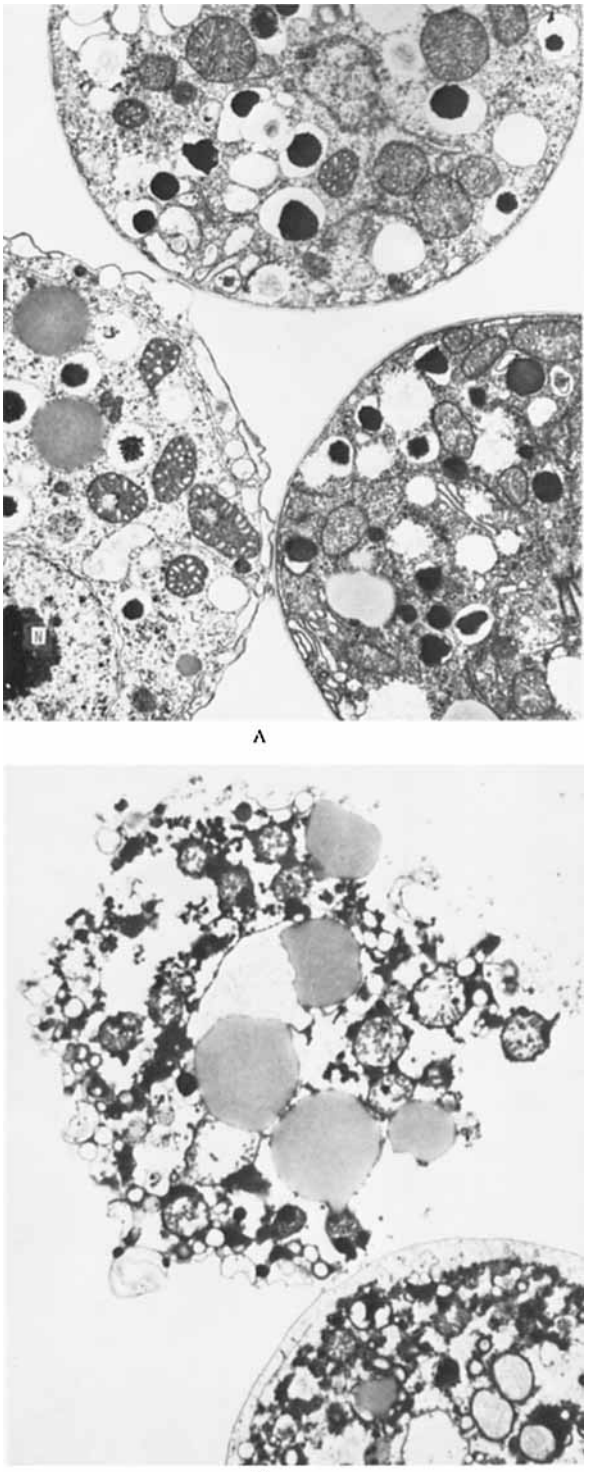


Fig. 16. Action of phaseolin *(18)* on zoospores of the soil fungus *Aphanomyces euteiches*, the cause of root rot in the pea. A) Two encysted zoospores and a non-encysted zoospore. The cell nucleus (N) and some organelles (control) can be recognized. B) Encysted and non-encysted zoospores 5 min after treatment with approximately 10^{-4} mol/l phaseolin. In both cases marked degenerative changes in the fine structure and disintegration of the ordered cell compartmentation are observed. The form of the encysted zoospores remains as the spore wall is not destroyed (magnification: ×25000. *H. C. Hoch, H. D. VanEtten* and *P. S. Matthews*, unpublished).

b) Do the phytoalexins appear at the sites within the plant where they could come into contact with the microorganism?

c) Are there any signs of an interaction between the phytoalexin and the microorganism?

d) Do other mechanisms play a role in the interaction between the host and the parasite and could this influence the growth of the parasite before the phytoalexins act?

The biological activity spectrum of the phytoalexins has been very extensively studied. The usual common bioassays make use of the phytoalexins fungitoxic action on spore germination, germ tube growth, radial mycelial growth on a solid nutrient medium or the accumulation of fungal mycelium in liquid culture. Isoflavonoid, terpenoid and polyacetylene phytoalexins inhibit a large number of pathogenic and non-pathogenic fungi in the above mentioned assays in concentrations of 10^{-5} to 5×10^{-4} mol/l[91,145–149,188]. The phytoalexins have been found to have fungistatic, fungicidic and in some cases also antibacterial properties[118,154,189]. *Hoch, VanEtten* and *Matthews*[191] examined cytological changes in zoospores of *Aphanomyces euteiches* which had been exposed to a phaseolin *(18)* solution. Figure 16 gives an impression of the action of this phytoalexin on the zoospores.

The fungitoxic properties measured *in vitro* can, however, vary greatly depending on the assay conditions[150–153, 188] and it is very difficult to evaluate the *in vivo* activity of the phytoalexins from these data. In many cases pathogenic fungi are insensitive to the phytoalexins of their hosts whereas non-pathogenic fungi are sensitive to the same phytoalexins[12,145,152,155,156,188]. Exceptions to this relationship between the pathogenicity of a fungus and its phytoalexin sensitivity have, however, also been described[91,107,156–159]. The tolerance of a fungus towards one or more phytoalexins of a certain plant as measured *in vitro* is thus not a prerequisite for the pathogenicity of the fungus towards this plant. The *in vitro* tolerance of fungi towards phytoalexins could be connected with the ability of the fungi to convert the phytoalexins into non-toxic compounds (see Section 4).

The *in vivo* situation in a host-parasite system is influenced by numerous factors. Of special interest are systems consisting of several varieties (cultivars) of a host plant and several differently pathogenic races of a microorganism in which some varieties of the host plant are susceptible and some are resistant (varietal specific resistance). The resistance reaction in such systems is often accompanied by the hypersensitive reaction in which some cells at the site of the infected plant tissue rapidly die, defense necroses are formed and phytoalexins accumulate. Examples of such host-parasite combinations are systems composed of several races of the fungus *Colletotrichum lindemuthianum* and varieties of bean *(Phaseolus vulgaris)*, of the fungus *Phytophthora megasperma* var. *sojae* (Pms) and soybean *(Glycine max)* as well as of the fungus *Phytophthora infestans* and potato *(Solanum tuberosum)*[23,150,158,160–163,169]. Although several races of the pathogenic agents are almost equally sensitive to the phytoalexins of their hosts[150,158,160] and the host varieties produce the same phytoalexins[23,150,169], some varieties of the host plant are susceptible and others are resistant. This varying behavior could be due to the fact that phytoalexin synthesis commences after different lag periods, proceeds at different rates and leads to different concentrations. Some observations showed that higher concentrations of phytoalexins were more rapidly

formed in incompatible combinations of host varieties and parasite races (*i.e.* with resistance) than in compatible combinations[150, 158, 160, 164, 169]. After the hypersensitive reaction had commenced in incompatible combinations with *C. lindemuthianum*, phaseolin *(18)* and related compounds accumulated in bean hypocotyls in concentrations which by far exceeded those required for *in vitro* inhibition of germ tube growth[150, 160, 164]. The accumulation of phaseolin and the appearance of necrotic cells were connected with restriction of fungal growth in the hypocotyls[165]. On the basis of these findings it is thought that the phytoalexins probably inhibit fungal growth in necrotic cells of bean hypocotyls but it also has to be remembered that phytoalexins could never come into contact with the germ tubes of *C. lindemuthianum*, or if so they would be too late to restrict their growth[24]. If the fungal metabolites of the phytoalexins which have been characterized *in vitro* can also be demonstrated *in vivo*, this will support the hypothesis that fungi invading the plants come into contact with their phytoalexins[2a].

Careful studies at the cellular level on the site of phytoalexin accumulation and distribution as compared with the distribution of the penetrating microorganism could help to solve this problem. Shortly after the germ tubes of *Botrytis cinerea* have entered the leaf cells of broad bean *(Vicia faba)*, the invaded cells and those in their immediate neighborhood become necrotic with the result that necrotic spots appear on the leaves within one day after innoculation. The distribution of *B. cinerea* is normally restricted to these first local lesions[166]. Fluorescence microspectroscopy showed that the vacuole content of the living cells in the vicinity of the necrotic cells had spectral properties similar to those of the isolated phytoalexins wyerone *(34)* and wyeronic acid *(33)*; these compounds accumulated in high concentrations in tissues infected with *B. cinerea* within two days[149, 167].

Comparative investigations using thin tissue sections were performed on the growth of the hyphae of *P. megasperma* var. *sojae* (Pms) and the local accumulation of glyceolin *(20)* in the area surrounding the spreading hyphae. These studies showed that the phytoalexin concentration in resistant soybean hypocotyls already exceeded the value required for the *in vitro* inhibition of fungal growth when the fungal growth had stopped in the soybean hypocotyls[178]. Similar findings were obtained from peppers *(Capiscum frutescens)* by measuring their capsidiol *(25)* content and by performing cell structural studies. According to these results the rate and extent of capsidiol formation in incompatible host-parasite combinations are more than sufficient to limit the infection[179–182]. Pepper, however, may be a special case; in ultrastructural studies a compatible interaction could be distinguished from an incompatible one only 4 h after innoculation with *Phytophthora capsici;* the fungus had not penetrated the cell wall and had not come into contact with the cytoplasm of the host cell[179, 183]. It seems possible that phytoalexin production in pepper is a secondary effect and that the specificity in this system is linked with the early stage of hypersensitivity or an as yet unknown factor[90a].

The experiments with the elicitors of phytoalexin synthesis demonstrate that they cannot determine varietal specificity in the Pms-soybean system. The elicitors isolated from virulent and avirulent Pms races and also living mycelium of these races are capable in all assays used, to induce glyceolin synthesis in soybean hypocotyls and cotyledons to a similar extent (Fig. 1)[121]. These results show that differences in the rates of glyceolin accumulation probably cannot account for resistance or susceptibility of the various soybean varieties towards different races of Pms.

Other findings, however, demonstrate that the elicitors are of importance for resistance. Soybean plants can be protected from a virulent Pms race if the elicitor is applied to the hypocotyl 6 h before innoculation with the mycelium of the virulent race. The elicitor cannot, however, protect the soybean plant if it is applied at the same time as the virulent Pms race. It is not known how the virulent race overcomes the inhibitory action of glyceolin. The widespread distribution of elicitors in nature[23, 118, 135] and their biological properties indicate that the elicitor concept is of general validity[118].

The ability to synthesize phytoalexins seems to be a widespread, effective means for plants to defend themselves against non-pathogenic microorganisms. As the examples of varietal-specific resistance (or susceptibility) show, phytoalexin formation does not, however, seem to be sufficient to protect plants against virulent races of microorganisms and against pathogenic microorganisms in general. It is not yet known which factors are responsible for the specificity of parasitism in plants. Earlier reports which state that the Pms elicitors of phytoalexin synthesis are the determinants of race specificity[168] contradict the findings discussed here[118].

In the following it will be indicated how it could be possible for pathogenic organisms to overcome the toxic effects of the phytoalexins. Conversion of phytoalexins by microorganisms to less toxic products has already been discussed in Section 4. Another possibility is that insensitivity towards the phytoalexins plays a role in the pathogenicity of some microorganisms. In neither case is it known whether the pathogenicity of the parasite is maintained on loss of its ability to metabolize the phytoalexins of the host plant or on loss of its insensitivity respectively. Finally, the phytoalexins could remain ineffective because the pathogenic agent does not come into contact with them during its development in the plant.

The pathogenic organism could also prevent the plant from synthesizing phytoalexins. It should be established whether the phytotoxins produced by pathogenic microorganisms[172–174] can be considered as effectors for such mechanisms. Other possible mechanisms would be inhibition of elicitor action by competitive factors[122] or inactivation of the elicitors before they reach their site of action in the plant cells. Terms such as "induction of susceptibility"[175] or "suppression of hypersensitive response and phytoalexin accumulation"[176] which have entered into the literature require a more detailed analysis of their significance at a molecular level.

6. Outlook

Phytoalexins have a wide spectrum of action against a large number of fungi and also against some bacteria and viruses. As yet there is no generally accepted opinion as to their importance in disease resistance of plants. The ability to synthesize phytoalexins seems to be an effective way in which plants can limit the growth of non-pathogenic microorganisms. In contrast, the contribution of phytoalexins in systems with varietal-specific resistance is still not clear; in these

systems the interactions between the host and the parasite are precisely controlled by genetic components[95].

The inducibility of phytoalexin synthesis is an interesting subject for studying the regulatory mechanisms of plant metabolism. Defined elicitors should be used in order to assess the possible involvement of inducer-receptor interactions and the reactions which they trigger in the redirection of metabolism. The questions which are raised concerning the processes at a molecular level which are connected with the stimulation of secondary plant metabolism are of fundamental importance for the understanding of gene expression in eukaryotic cells[186]. In the future, elicitors could also find practical application for the "induced protection" of plants against disease. The phytoalexins, which include different groups of natural substances, may finally provide a stimulus for conceiving novel, non-polluting pesticides.

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Protein Biosynthesis: The Codon-Specific Activation of Amino Acids

By Eggehard Holler[*]

Dedicated to Professor Hermann Hartmann

At the start of protein biosynthesis the amino acids are chemically activated by esterification with transfer ribonucleic acids bearing the appropriate anticodons. The esterification is catalyzed with an exceptionally high specificity by aminoacyl-tRNA synthetases. Current knowledge of the structural properties of the reactants, the course of the reaction, and the reasons for its specificity are summarized.

1. Introduction

The function of transfer ribonucleic acids (tRNA) in protein biosynthesis is to convey amino acids to the ribosomal synthetic apparatus in an order which is dictated by messenger ribonucleic acid (mRNA) (see Fig. 1). The esterification of the amino acids by tRNA activates their carboxy groups; the tRNA anticodon characteristic for each amino acid is responsible for the translation of the nucleic acid code into an amino acid sequence of the growing peptide. This translation is extremely accurate. The chance incorporation of L-valine instead of L-isoleucine into a mammalian hemoglobin chain shows that the resulting amino acid sequence corresponds with the genetic "template" in at least 99.97% of the cases[1].

Ester formation between the amino acids and the tRNA is catalyzed by aminoacyl-tRNA synthetases. They are the central topic of the present article. For earlier reviews see ref. [2].

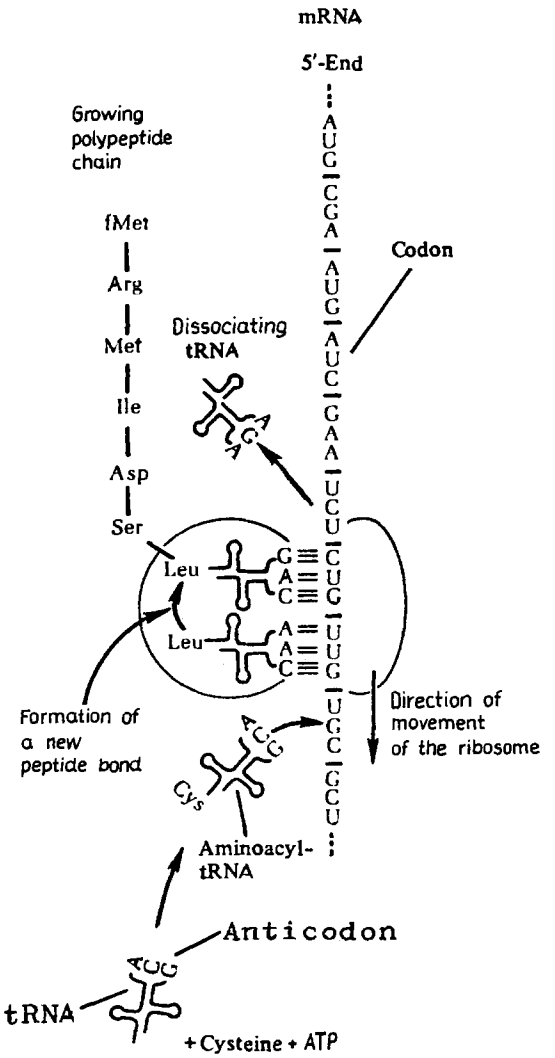


Fig. 1. The important steps of protein synthesis.

2. Aminoacyl-tRNA Synthetases

2.1. Occurrence

In bacterial cells, an individual aminoacyl-tRNA synthetase is assigned to each amino acid. In plant and animal cells, the enzymes of the cytoplasm and the organelles (mitochondria and chloroplasts) are not identical. They preferentially aminoacylate only the tRNA of the same compartment. Cytoplasmic synthetases form larger, apparently membrane-bound complexes with molecular weights approaching 10^6[3].

The intracellular concentrations of aminoacyl-tRNA synthetases and of tRNA in bacterial cells are of the order of 10^{-6} mol/liter. No estimates can be made for plant and animal cells because of compartmentation. It can be deduced from the values of the concentrations and dissociation constants that a considerable portion of the synthetases is complexed with the tRNA. However, recent findings seem to indicate that most of the tRNA is aminoacylated and complexed with the ribosomal elongation factor EFTu.

2.2. Structure

Synthetases consist of a single peptide chain (α type), of two identical (α_2 type), or of two non-identical chains ($\alpha\beta$ type), and of pairs of non-identical chains ($\alpha_2\beta_2$ type). Single- or double-chain synthetases have molecular weights in the region of 46000 to 140000; the molecular weights of the tetrameric synthetases are of the order of 220000 to 290000. The synthetases have a predominantly dimeric structure if the tetrameric enzyme is considered as $(\alpha\beta)_2$. The tertiary

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structures of the monomeric synthetases consist of globular folded subregions (domains). Some regions have repeating amino acid sequences[4]. The homologous sequences most probably originate from the duplication and fusion of single, ancestral genes.

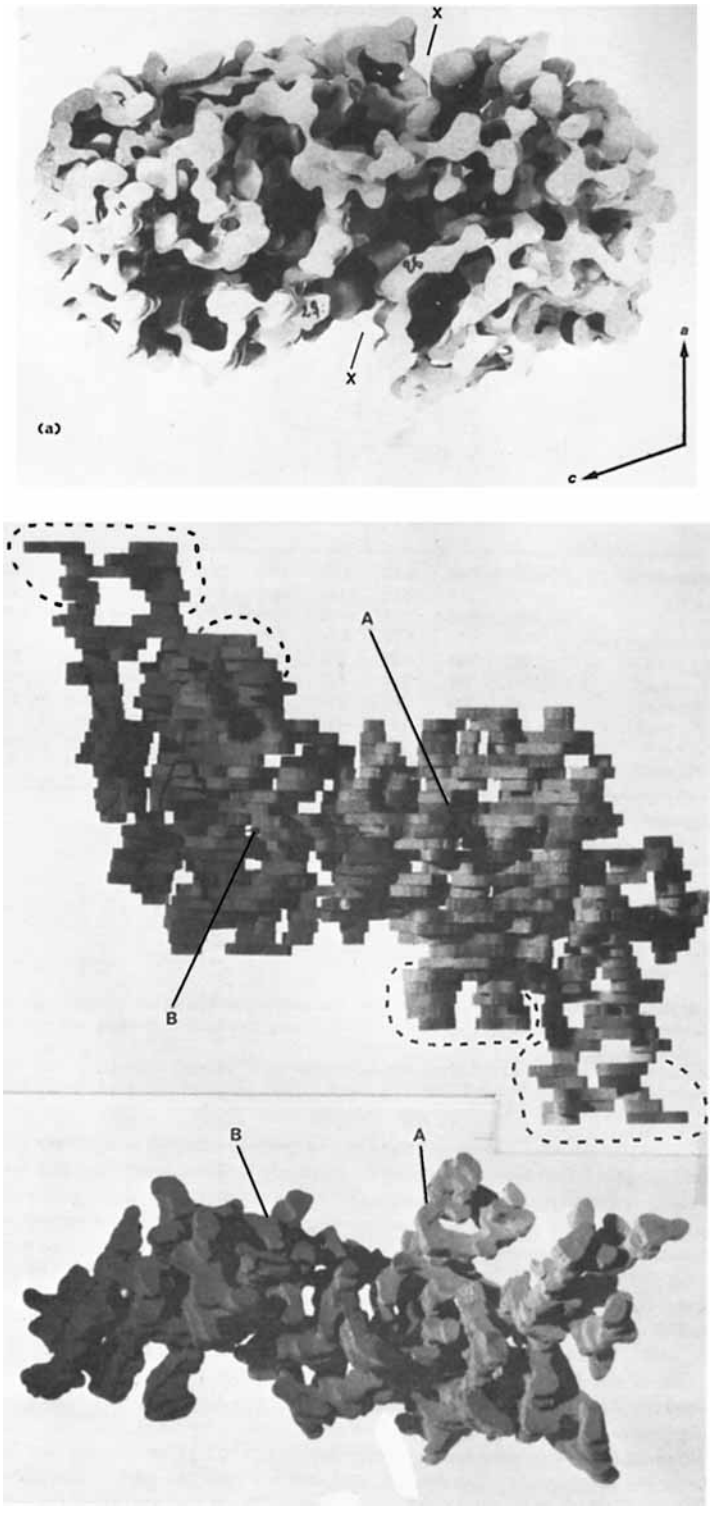


Fig. 2. Structural models of two aminoacyl-tRNA synthetases based on X-ray crystallographic studies. (a) Proteolytic fragment of methionyl-tRNA synthetase from *E. coli* at a resolution of 4 Å [6]. The fragment is an enzymatically active monomer and has a molecular weight of 64000. Native methionyl-tRNA synthetase is a dimer and has a molecular weight of 172000. The fragment is composed of two domains which are covalently linked at their contact surfaces (X—X). (b) Two orthogonal views of a structural model for tyrosyl-tRNA synthetase at a resolution of 3.5 Å [5]. The enzyme is a dimer and has a molecular weight of 90000. The components encircled by dashed lines are mobile and their positions cannot be determined precisely. The two active centers are located at A and B.

X-Ray structure analysis has been performed on the tyrosyl-tRNA synthetase from *Bacillus stearothermophilus* with a resolution of 2.7 Å, and on the tryptic (enzymatically active) fragment of the methionyl-tRNA synthetase from *Escherichia coli* with a resolution of 4 Å[5, 6] (Fig. 2). In the case of the latter enzyme, the X-ray small-angle scattering has also been measured[7]. The common result of these studies is that the synthetases have a less compact structure than do other enzymes. The monomer of the tyrosyl-tRNA synthetase (MW 45000) occupies a volume of 60×40 Å^3 and the dimer has a maximum extension of 130 Å.

As is the case with other enzymes made up of identical subunits, aminoacyl-tRNA synthetases exhibit negative cooperativity[*] for substrate binding and half-of-the-sites reactivity[**][8–10]. In the $\alpha_2\beta_2$ type proteins, the problem arises as to how the substrate binding sites or active centers should be assigned to the different subunits. Results obtained with the phenylalanine-specific system of *E. coli* support the notion that complex formation with the amino acid and with the tRNA occurs at different subunits[11]. In the glycine-specific system of *Bacillus brevis* the smaller subunit (α) only catalyzes amino acid-dependent ATP-[^{32}P]pyrophosphate exchange (see Section 4.2), whereas the complete enzyme ($\alpha_2\beta_2$) is needed for aminoacylation of tRNA[12].

With the exception of the lysine-specific system of *E. coli*, the aminoacyl-tRNA synthetases are reversibly inhibited by substances which react with sulfhydryl groups [mercury(II) or disulfide compounds] and are irreversibly inhibited by alkylating agents. At the same time unfolding of the protein is frequently observed which, in the case of enzymes with quaternary structures, is paralleled by a dissociation into the subunits[13]. Sulfhydryl groups are not considered to be essential for the catalysis.

Histidine-specific reagents such as diethyl pyrocarbonate and rose bengal (photochemical oxidation) were found to inhibit the catalytic function of the phenylalanine-tRNA synthetase from *E. coli*[14]. Prolonged incubation also led to a dissociation into subunits. Lysine side chains have been found to be involved in the anchorage of ATP[68].

Metal ions can stabilize the protein structure and activate the enzyme[9, 15]. The effective concentration range of Mg^{2+} for phenylalanyl-tRNA synthetase is found to be between 10^{-4} and 10^{-2} M.

The enzymatic activity of aminoacyl-tRNA synthetases in mammalian tissues is regulated by a hormone-controlled phosphorylation/dephosphorylation[16].

2.3. Catalysis

The reactions catalyzed by aminoacyl-tRNA synthetases consist of amino acid activation [equation (a)] and amino acid transfer [equation (b)].

[*] Negative cooperativity is observed in enzymes which are composed of identical or similar protein chains. These have identical or similar binding sites for the same substrate. The tendency for forming an enzyme-substrate complex is the same at each binding site as long as one of the sites is not already occupied by a substrate molecule. As more substrate binds to the enzyme the affinity to bind at the other sites that are still free decreases.

[**] Half-of-the-sites reactivity occurs if only half of the number of the active sites of an enzyme are catalytically active.

$$MgATP + AA + E^{AA} \rightleftharpoons E^{AA}\cdot AA \sim AMP + MgP_2O_7^{2-} \quad (a)$$
$$E^{AA}\cdot AA \sim AMP + tRNA^{AA} \rightleftharpoons E^{AA} + AA - tRNA^{AA} + AMP \quad (b)$$

AA signifies the amino acid, E^{AA} the specific synthetase, and $tRNA^{AA}$ the codon-specific tRNA. Adenosine 5'-triphosphate only acts as a substrate when combined with Mg^{2+} (*i.e.* MgATP). The products of the two reactions are magnesium pyrophosphate ($MgP_2O_7^{2-}$), adenosine 5'-monophosphate (AMP), and the aminoacyl-tRNA (AA-$tRNA^{AA}$).

During amino acid activation [equation (a)], the amino acid (AA) and MgATP associate with the active center of the synthetase (E^{AA}) in a sequence which is probably kinetically but not obligatorily ordered. The primary association step is followed by a possibly multistep rearrangement of the complex in which the amino acid carboxylate group approaches the triphosphate residue of the ATP after overcoming the electrostatic repulsion. At the same time the anhydride bond P_α—O—P_β of the ATP is polarized in the direction of the pyrophosphate cleavage; the production of the aminoacyl adenylate (AA ~ AMP) is thus finally facilitated. The free energy that is required to enforce the juxtaposition of the negatively charged groups (7 to 10 kcal/mol depending on the kind of synthetase) is obtained during the formation of the secondary bonds (electrostatic and hydrophobic interactions, as well as hydrogen bonds) between the enzyme and the substrates during the rearrangement of the enzyme·substrate complex. As a result, the synthesis of the synthetase·aminoacyl adenylate-$MgP_2O_7^{2-}$ complex as given in equation (c) is favored over reaction (d) by several kcal/mol[17–19].

$$E^{AA}\cdot AA\cdot MgATP \rightleftharpoons E^{AA}\cdot AA \sim AMP\cdot MgP_2O_7^{2-} \quad (c)$$
$$AA + MgATP \rightleftharpoons AA \sim AMP + MgP_2O_7^{2-} \quad (d)$$

The aminoacyl adenylate (AA ~ AMP), which is highly labile in its free form, remains associated with the synthetase (binding constant 10^9 liter/mol) on account of its tendency to form complexes. $MgP_2O_7^{2-}$ is liberated and hydrolyzed by another enzyme to orthophosphate. This causes the equilibrium to shift in the direction of adenylate formation.

The synthesis of the intermediate is followed by transfer of the amino acid residue to the 2'- or 3'-hydroxy group of the 3'-terminal ribose residue of the tRNA depending on the kind of synthetase[20]. It is not known whether a covalent aminoacyl synthetase is formed as intermediate[21]. The transfer is followed by a rapid 2',3'-isomerization (half-time of 0.3 s for leucyl-tRNA)[22]. It is an open question whether the isomerization takes place in the complex or after dissociation of the aminoacyl-tRNA from the enzyme. The primary acylation site was identified by the use of transfer ribonucleic acids with 2'- or 3'-deoxyribose in the terminal position.

The final step in the catalysis is the dissociation of the aminoacyl-tRNA from the enzyme. The dissociation constants for the tRNA (substrate) and the aminoacyl-tRNA (product) are of similar magnitudes (10^{-7} to 10^{-6} mol/liter). The enzyme kinetics show product inhibition.

What are the rates with which the elementary steps described above follow one another? Table 1 gives a summary. Rapid formation of the complex between the synthetase and the substrates is followed by a more time-consuming synthesis of the aminoacyl adenylate intermediate and then by the considerably slower transfer of the aminoacyl residue to the tRNA. This step is limiting in most systems under steady state kinetic conditions. The phenylalanine-specific system of *E. coli* is an exception, since here a rearrangement of the synthetase·phenylalanyl-tRNA complex appears to be the rate-limiting step[23].

2.4. The Problem of Product Inhibition

In an enzymatic synthesis, the problem of competitive inhibition[*] by a product X—Y arises if this product consists of fragments of the substrates X and Y and if the substrates associate with the synthetase *via* the same fragments (Fig. 3). The dissociation constant for the complex between the enzyme and the reaction product is then approximated by

$$K_{X-Y} = (1/55)\cdot K_X \cdot K_Y$$

where K_X and K_Y are the dissociation constants for the complexes between the enzyme and the substrates X and Y. The factor $^1/_{55}$ results from the choice of the thermodynamic standard condition (1 M aqueous solution).

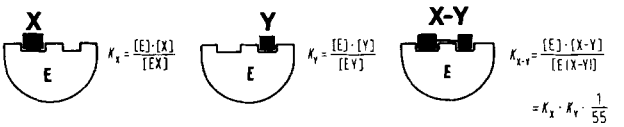


Fig. 3. Calculation of the dissociation constant K_{X-Y} for a complex between an enzyme and the ligand X—Y using the dissociation constants K_X and K_Y of the complexes with the fragments X and Y. The example given is simplified: the complexes EX and EY are held together by the same secondary bonds as the complex E(X—Y). The factor $^1/_{55}$ results from reference to standard thermodynamic conditions (1 M aqueous solution) [43].

Aminoacyl-tRNA synthetases form tight complexes with their substrates (amino acids and tRNA). According to the equation for K_{X-Y}, they should form an even tighter complex with the product (aminoacyl-tRNA) and thus be competitively inhibited at very low product concentrations (10^{-10} to 10^{-12}

[*] Competitive inhibition occurs when the inhibitor (in the present case the product) competes with the substrate for the binding site on the enzyme.

Table 1. Rate constants for the elementary steps of amino acid activation and transfer. Measurements were performed at 25°C, pH = 7 to 8, with an ionic strength of 0.05 to 0.2 mol/liter and a magnesium concentration of 0.001 to 0.01 mol/liter.

Direction	Complex formation of synthetase with			Adenylate formation [equation (c)]	Aminoacyl transfer [equation (b)]	Overall reaction under steady-state conditions
	AA	MgATP	$tRNA^{AA}$ or AA-$tRNA^{AA}$			[equations (a) + (b)]
→	[liter/(mol·s)] 10^6	[liter/(mol·s)] 10^6	[liter/(mol·s)] $(1-3)\times 10^8$	20—350	2—28	2—6
←	[s^{-1}] 15—25	[s^{-1}] 400 [17]	[s^{-1}] 5—120	30—1000	10 [23]	10 [23]

mol/liter depending on the kind of synthetase). However, the aminoacyl-tRNA has been found to have the same tendency to form a complex with the enzyme as has the (free) tRNA. The aminoacyl residue thus does not seem to contribute to the stability of the enzyme·aminoacyl-tRNA complex. The amino acid and tRNA fragments in the aminoacyl-tRNA complex cannot associate simultaneously with the amino acid and tRNA binding sites for steric and/or energetic reasons (Fig. 4). After transfer of the amino acid residue to the tRNA, the unstable complex *(2)* is only formed as an intermediate. Interaction between the synthetase and the amino acid residue is eliminated by the subsequent rearrangement *(2)→(3)*. It is interesting that this rearrangement is rate-limiting for phenylalanyl-tRNA synthetase from *E. coli*[23].

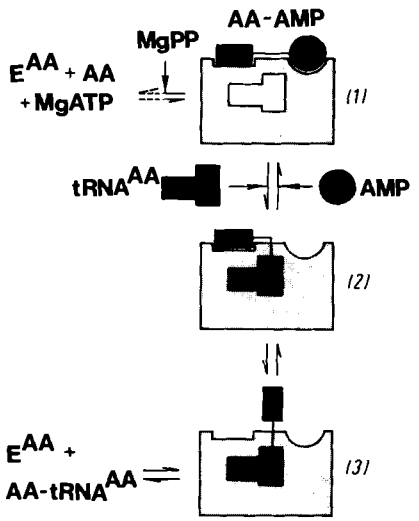


Fig. 4. Reaction scheme for the transfer of an amino acid residue from AMP to tRNA and the dissociation of the aminoacylated tRNA. The enzyme is shaded in gray. The substrates and their components are black (amino acid: rectangle, AMP: circle, $tRNA^{AA}$: T-shaped symbol). The transfer of the amino acid residue to the tRNA takes place in step *(1)→(2)*. The complex *(2)* is unstable because the amino acid and the tRNA fragments cannot complex with the synthetase at the same time for steric and/or energetic reasons. It rearranges to complex *(3)* with the dissociation of the amino acid residue from the amino acid binding site.

The energetics leading to the elimination of the interaction between the enzyme and the amino acid residue are shown in Figure 5; the free energy is schematically represented as a function of the reaction coordinate. The synthetase·amino acid·MgATP complex is utilizing free energy to establish the special geometry of the enzyme·substrate complex. This energy becomes available when the aminoacyl adenylate is synthesized because the electrostatic and/or steric arrangement is reorganized. This energy is not released but is picked up for the synthesis of the aminoacyl adenylate[9, 17, 24].

The group transfer potential[*] of the aminoacyl-AMP is 14 kcal/mol[25] and that of the aminoacyl-tRNA 7 kcal/mol[26]. On transfer of the aminoacyl residue from AMP to the tRNA 7 kcal/mol are thus liberated. This amount of free energy causes the observed destabilization of the synthetase·aminoacyl-tRNA complex by expelling the aminoacyl residue from the enzyme binding site.

[*] The group transfer potential of a compound A—B is identical with the value of the standard free energy measured on hydrolytic cleavage of A—B to A—H and B—OH under standard conditions (pH = 7.0, 25°C, ionic strength 0.1 mol/liter).

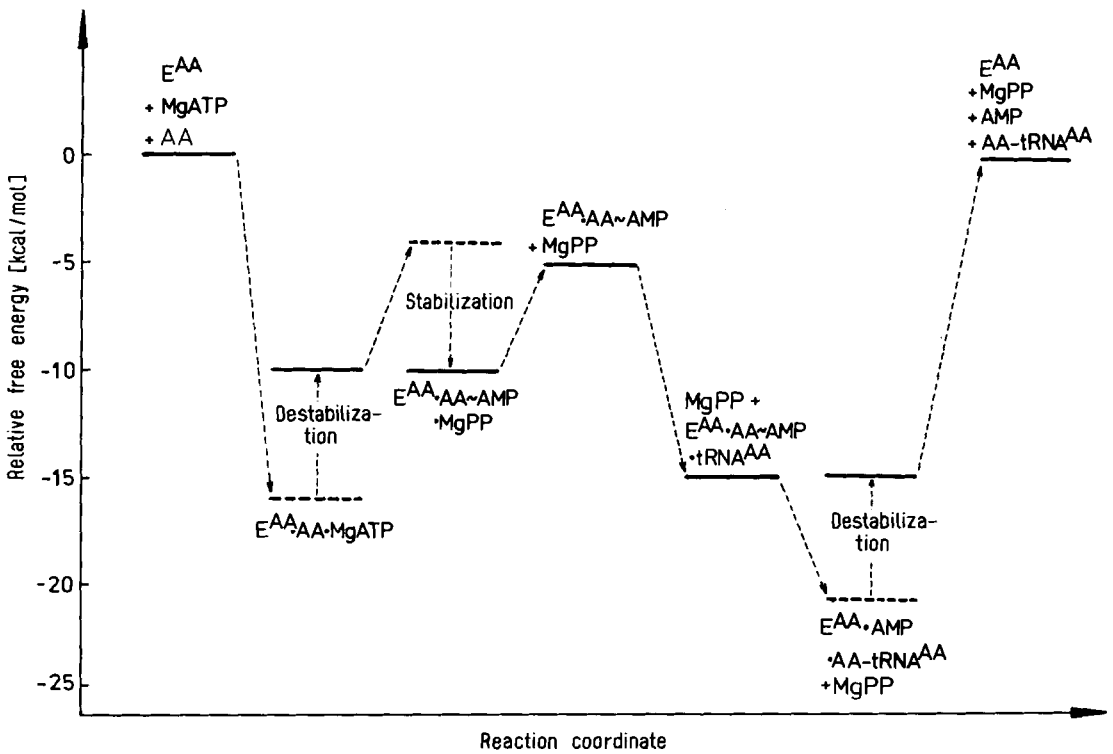


Fig. 5. Free energy of the catalytic pathway as a function of the reaction coordinate of tRNA aminoacylation. The formation of the synthetase·substrate, synthetase·intermediate and synthetase·product complexes is shown. Activated transitional complexes have been omitted. The levels denoted by dashed lines represent the hypothetical case where the secondary bonds between the synthetase, amino acid and MgATP or aminoacyl-tRNA are not used as a supply for the energy consuming orientation of the ligands in the complex. The complex between the synthetase and the substrate fragments was taken as a basis for calculating the values. The numerical values refer to the phenylalanine-specific system of *Escherichia coli* [9].

3. Transfer Ribonucleic Acids

3.1. Occurrence and Function

Transfer ribonucleic acids are components of the cytoplasm and of the cell organelles (mitochondria and chloroplasts). Like the aminoacyl-tRNA synthetases they exhibit a compartment-specific differentiation. They are the codon-specific "suppliers" of activated amino acids in ribosomal protein biosynthesis. Some species of tRNA serve as amino acid "suppliers" in the non-ribosomal synthesis of bacterial cell walls[27] and the maturation of proteins and phosphatides[28]. Transfer ribonucleic acids are involved in the regulation of the synthesis of certain enzymes[29]. A tryptophan-specific tRNA is used as a primer[*] of DNA synthesis in the presence of RNA-dependent DNA-polymerase[30]. A tRNA-like structure which can be aminoacylated is found at the 3'-end of plant virus RNA[31].

3.2. The Clover Leaf Structure

Transfer ribonucleic acids have an average molecular weight of 25000 and are composed of 73 to 93 ribonucleosides some of which are modified in the mature[**] tRNA. The nucleotide sequences of more than sixty tRNAs are known. All transfer ribonucleic acids have the same secondary structure which is called the "clover leaf" structure on account of its appearance (Fig. 6).

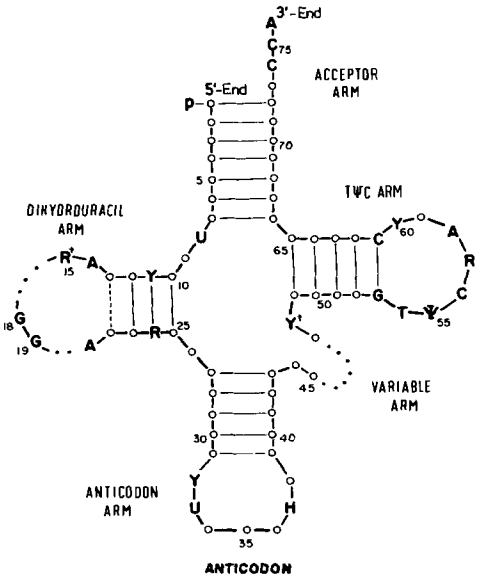


Fig. 6. Secondary structure (clover leaf structure) of transfer ribonucleic acids (not including initiator-tRNA). The bases are numbered with reference to the structure of yeast $tRNA^{Phe}$. Y signifies pyrimidine, R purine, and H hypermodified purine. The sequences denoted by dots are of variable length. The figure is taken from a review article [32].

Beginning at the 5'-terminus, all transfer ribonucleic acids have an "amino acid acceptor stem" that consists of 7 base pairs. This region is followed by the "dihydrouracil" stem with 3 or 4 base pairs, the anticodon stem with 5 base pairs, and the TΨC stem with 5 base pairs. The base pairs are held together by Watson-Crick-type hydrogen bonds[*]. There are always two nucleotides between the amino acid acceptor stem and the dihydrouracil stem and a single nucleotide between the dihydrouracil and anticodon stems. The nucleic acid forms loops at the ends of the stems. The loops can be imagined to form the leaflets of the clover leaf. The anticodon and TΨC loops are each composed of 7 nucleotides and the dihydrouracil loop of 7 to 10 nucleotides. Each stem plus loop constitutes an "arm". The variable (or extra) arm has 4 to 21 nucleotides.

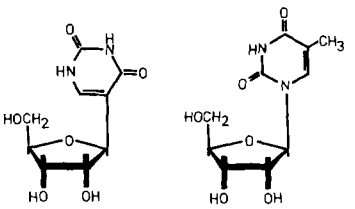


Fig. 7. The modified nucleotides pseudouridine and ribothymidine are components of all transfer ribonucleic acids with the exception of mammalian initiator-tRNA.

The modified nucleosides ribothymidine (T) and pseudouridine (Ψ) (Fig. 7) are components of all transfer ribonucleic acids apart from the initiator tRNA of mammals. The sequence G—T—Ψ—C is believed to associate with the 5S ribosomal RNA of bacterial ribosomes during the elongation phase of protein synthesis.

The anticodon consists of three variable nucleotides located in the middle of the anticodon loop. On complex formation with the ribosome it associates with the appropriate codon of the messenger RNA.

The single-stranded amino acceptor terminus has an identical nucleotide sequence, —CCA, in all transfer ribonucleic acids.

3.3. Tertiary Structure

The three-dimensional structure (tertiary structure) of the phenylalanine-specific tRNA ($tRNA^{Phe}$) of yeast is shown in Fig. 8. The diagram is the result of X-ray diffraction (2.5, 3, and 4 Å resolutions) and X-ray small-angle scattering analysis as described in review articles[32,33].

The tertiary structure has the following characteristics: 1) $tRNA^{Phe}$ is L-shaped; 2) The stems are composed of double helices; 3) The amino acid acceptor stem and the TΨC stem are stacked upon each other making them appear to form a single double helix. The same is found for the dihydrouracil stem/anticodon stem; 4) The CCA terminus and the anticodon are at the ends of the "L"; 5) The dehydrouracil and TΨC loops form the corner of the "L".

The tertiary structure is mainly the result of interactions between the dihydrouracil arm, the TΨC arm, and the variable arm (*i.e.* those arms in the corner of the "L"). The interactions

[*] A primer is a short nucleic acid strand which is associated with the longer template strand. The synthesis of the daughter strand complementary to the template joins on at the 3'-end of the primer.

[**] tRNA is formed by "maturation" of precursors which are synthesized by gene transcription. During maturation, the precursors are cut to the sizes of tRNA by nucleases and are chemically modified at some of the bases by specific enzymes.

[*] Watson-Crick hydrogen bonds are those between the bases guanine/cytosine and adenine/thymine in the double helix of DNA and between the bases guanine/cytosine and adenine/uracil in the double helix of RNA.

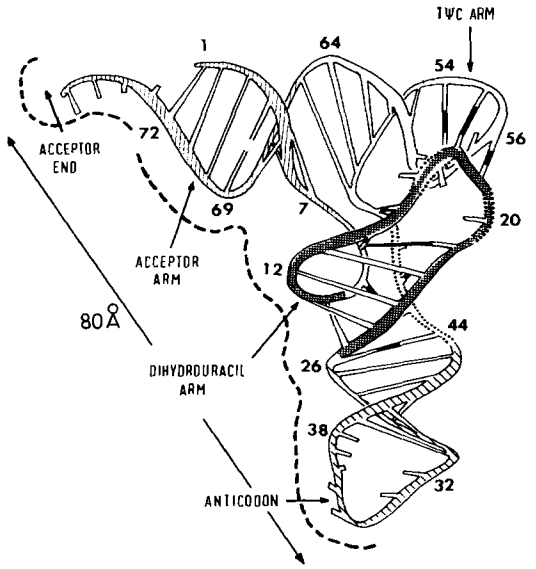


Fig. 8. Schematic representation of the three-dimensional structure (tertiary structure) of yeast $tRNA^{Phe}$. The ribose-phosphate strand is shown by a continuous band. The hydrogen bonds are represented by bars. The arms of the tRNA are denoted by different hatchings. The sequences marked by dotted lines differ in length depending on the type of tRNA. The dashed line shows the surface of the molecule that is in contact with the aminoacyl-tRNA synthetase. The figure is taken from a review article [50].

include: 1) Hydrogen bonds between bases, between bases and ribose residues and between different ribose residues; 2) Electrostatic repulsion between phosphate groups; 3) Coordination with Mg^{2+}. The electrostatic repulsion destabilizes the tertiary structure. Electrolytes such as NaCl improve the stability by shielding of the negative charges[34,35]. Under physiological conditions the tertiary structure is probably modulated on formation of the complexes with the reaction partners (aminoacyl-tRNA synthetase, ribosomal elongation factor EFTu or the ribosome).

Studies on other transfer ribonucleic acids indicate that they also possess the properties described above. Findings for the aqueous solution agree with those for the crystal structure.

4. The Codon-Specific Recognition of Amino Acids and Transfer Ribonucleic Acids by the Aminoacyl-tRNA Synthetases

During the aminoacylation of tRNA, every aminoacyl-tRNA synthetase must select the only amino acid from the twenty kinds present in the cell that matches the cognate tRNA. High precision is necessary as the ligation between the amino acid and the tRNA is not checked again during the later stages of protein synthesis. A mistake made during amino acid activation may thus result in a defective protein molecule.

Whether the amino acid and the tRNA that have been selected by the synthetase are the correct ones is checked and verified several times during the synthesis of the aminoacyl-tRNA (see Fig. 9), namely on formation of the enzyme·amino acid complex, at the level of the enzyme·aminoacyl adenylate complex, and by hydrolytic "proofreading" after formation of the enzyme·aminoacyl-tRNA complex.

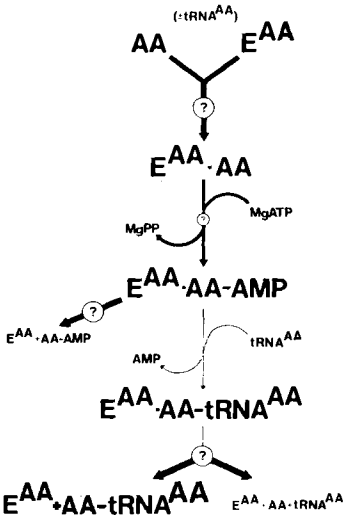


Fig. 9. Verification of matching anticodon and amino acid. The steps which represent a barrier for the codon-mismatching amino acids are indicated by question marks and their importance is represented by the width of the arrows. The discriminatory reaction steps are, from top to bottom: formation of the enzyme·amino acid complex, synthesis of the aminoacyl-adenylate, stability of the synthetase·aminoacyl adenylate complex and corrective hydrolysis of the misacylated tRNA.

4.1. Recognition of the Amino Acid

The most efficient step in "sieving" for the cognate amino acid is the formation of the synthetase·amino acid complex. According to the structural elements of an amino acid, the aminoacyl-tRNA synthetases have binding regions for the primary ammonium group, for the carboxylate group, and for the side chain[19,36]. Apart from a few exceptions[37], recognition is stereospecific with respect to the configurations at C-2 and C-3.

The interaction between the zwitterionic region of the amino acid and the synthetase is electrostatic[19]. Complex formation with the side chain of the amino acid is, depending on the nature of the side chain, a result of polar or hydrophobic interactions. Hydrophobic mechanisms are employed particularly for the recognition of aliphatic amino acids[17,38,39]. In the case of the isoleucine-specific system it has been shown that the "correct" amino acid has the highest association entropy[40].

Discrimination between related amino acids such as L-tyrosine and L-phenylalanine or L-isoleucine and L-valine depends on the interaction between the aminoacyl-tRNA synthetases and the characteristic components of the side chains such as the OH group in L-tyrosine and the additional CH_3 group in L-isoleucine. The degree of discrimination is extremely high; L-tyrosine is preferred over L-phenylalanine by a factor of 2000 and L-isoleucine over L-valine by a factor of 100. Such differences in affinity cannot be accounted for by simple models involving solely hydrogen bond formation or interactions between hydrophobic moieties[17,18]. As in the isoleucine-specific system[17], conformational changes in the enzyme structure that could lead to a solvation of newly exposed residues might be of importance.

Binding studies with substrate fragments have shown that the triphosphate moiety of MgATP and the zwitterionic region of the amino acid interact with one another in the ternary

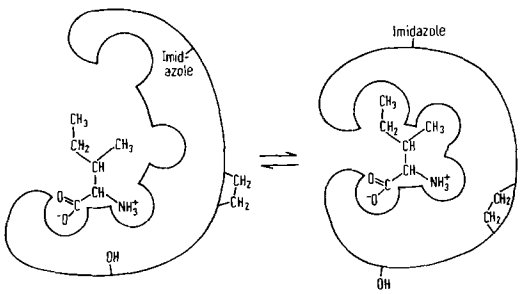


Fig. 10. Schematic representation of a structural change that could increase the tendency for forming the enzyme·amino acid complex. The binding of the substrate L-isoleucine to the synthetase is coupled with a conformational change. This causes an alteration in the hydration of the synthetase, which is here arbitrarily represented by exposure of an imidazole residue and of a hydroxy group, together with the transfer of an ethylene group into the interior of the enzyme structure.

enzyme·substrate complex[19,24]. The electrostatic attraction between the α-ammonium group and the triphosphate residue stabilizes the complex and the electrostatic repulsion between the carboxylate group and the triphosphate residue destabilizes it. The sizes of these opposing interactions are such that they cancel each other out and both the amino acid and the MgATP apparently associate with the synthetase independently of one another[19][*].

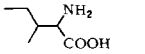
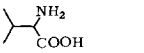
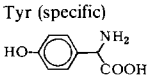
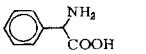
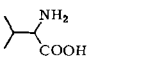
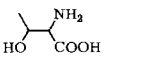
4.2. Thermodynamic Control of Formation of the Enzyme·Aminoacyl Adenylate Complex

Table 2 shows that the dissociation constant

$$K_{Diss} = \frac{[E^{AA}][AA]}{[E^{AA} \cdot AA]}$$

for the enzyme-substrate complex formed in the first step of the amino acid activation is, in the case of the amino acid pair isoleucine/valine, two orders of magnitude smaller for the codon-specific amino acid (isoleucine) than for the nonspecific amino acid. The Michaelis-Menten constants for the ATP-[^{32}P]pyrophosphate exchange[**] of other pairs are compared in Table 2; under the experimental conditions used[41], the values are the same as those of the Michaelis-Menten constants K_m^{AA} for amino acid activation and approximately the same as the dissociation constants K_{Diss}. In the case of the amino acid pairs tyrosine/phenylalanine and valine/threonine it can be seen that the synthetase·amino acid complex of the codon-specific amino acid is thermodynamically favored by several orders of magnitude.

Table 2. Dissociation constants, Michaelis-Menten constants, and relative rate constants for the amino acid activation of pairs of structurally similar amino acids.

Amino acid	K_{Diss} [μmol/liter]	ATP-[^{32}P]pyrophosphate exchange K_m [μmol/liter]	k (relative)
Ile (specific)	4.5 [64]	4—6 [41, 42, 66]	1.0
	5.8 [17]	42, 66] 5 [67]	
Val	570 [64]	800 [67]	0.77 [67]
			
Tyr (specific)	10 [65]	1.8 [65]	1.0
		25 [37]	
Phe		50000 [65]	0.4 [65]
			
Val (specific)	66 [66]	140 [39]	1.0
		30 [38]	
Thr		17000 [39] 7000 [38]	0.38 [39] 0.42 [38]
			

This situation is further improved by the amino acid concentrations which exist in the cell: if the specific amino acid competes with a nonspecific amino acid for the synthetase then the operational dissociation constant $K^u_{Diss(app)}$ of the complex with the nonspecific amino acid is given by

$$K^u_{Diss(app)} = K^u_{Diss}\left\{1 + \frac{[AA]}{K^{AA}_{Diss}}\right\}$$

i.e. the chance of the nonspecific acid forming the "wrong" synthetase·amino acid complex is lower the higher the concentration [AA] of the "correct" amino acid.

The specificity is further improved by the fact that, during the catalytic aminoacylation of the tRNA, the "correct" amino acid binds very tightly with the synthetase in the form of its aminoacyl adenylate complex and thus again reduces the chance of an association between the enzyme and a "wrong" amino acid. Any enzyme·aminoacyl adenylate complex containing a "wrong" amino acid is removed by hydrolysis[44] or by esterification with the tRNA and subsequent hydrolytic "proofreading"[38] (see Section 4.4).

4.3. Recognition of the Transfer Ribonucleic Acid

The interactions between the enzyme and the tRNA are mainly a result of the formation of hydrogen bonds between the amino acid side chains of the synthetase (Asn, Gln, and Arg) and the purine bases of the tRNA[45]. "Stacking" interactions between the bases and the aromatic side chains of the amino acids are less important. It is not clear whether Mg^{2+} ions stabilize the enzyme·tRNA complex by interacting between the surfaces of the synthetase and the tRNA which

[*] The electrostatic repulsion between the triphosphate group and the carboxylate group, and the strain-inducing interaction between the triphosphate moiety and the MgATP binding site are the reason for the synthetase·amino acid·MgATP complex having a relatively high energy content (see Fig. 5). The "internal strain" of the ternary complex is released by the reaction producing the enzyme·aminoacyl adenylate complex.

[**] By following the ATP-[^{32}P]pyrophosphate exchange, the reverse of amino acid activation [equation (a)] (*i.e.* reaction of the synthetase·aminoacyl adenylate complex with [^{32}P]pyrophosphate) is measured. The system is in chemical equilibrium. At sufficiently high pyrophosphate concentrations, the rate of synthesis of the aminoacyl adenylate also determines the rate of [^{32}P]-labeling of the ATP. The ATP-[^{32}P]pyrophosphate exchange is thus an indirect measurement of the formation of the synthetase·aminoacyl adenylate complex.

come into contact with one another[46-48] or whether Mg^{2+} selectively stabilizes the tertiary structures of the enzyme and tRNA which form particularly strong complexes with one another[9,15,49].

The synthetase and transfer ribonucleic acid in the enzyme·tRNA complex come into contact along the angled side of the L-shaped tRNA molecule (Fig. 8)[50], probably along a cleft on the protein surface. The binding region of the tRNA is formed by components of the acceptor stem and the dihydrouracil stem and in some cases by the anticodon. The TΨC arm and the variable arm do not touch the synthetase. Most of the variable bases are found in the regions of the contact sites.

The acceptor end —CCA is thought to play a key role in recognition of the tRNA by the synthetase, the mechanism of which is unknown[51]. This region probably changes its conformation on aminoacylation[52].

The formation of the synthetase·tRNA complex in some systems is coupled with the formation of the enzyme·amino acid and/or enzyme·MgATP complex. Depending on the nature of the synthetase, the coupling exhibits positive[53] or negative cooperativity[9,10,54]. In some cases when the enzyme has a dimeric structure, coupling appears only if both of the active centers are occupied by the substrates.

The association resulting in the synthetase·tRNA complex proceeds in two stages[49,55]. Initially, a relatively unspecific diffusion-controlled complex is formed which, on developing probably specific secondary bonds, rearranges to give the stable enzyme·substrate complex. In the glutamine- and phenylalanine-specific systems, formation of the enzyme·tRNA complex is accompanied by a rearrangement of the tRNA molecule[56].

Discrimination between the "correct" and the "wrong" transfer ribonucleic acids depends much more on kinetic control than on the thermodynamic properties of the enzyme·tRNA complex[57]; the "correct" amino acid is 10^3 to 10^4 times more rapidly aminoacylated than the "wrong" one.

4.4. Hydrolysis of Misacylated tRNA

In spite of the "precautions" described above, transfer ribonucleic acids are occasionally acylated with a "wrong" amino acid. This misacylation is more frequent the greater the similarity between the amino acids.

A wrongly loaded aminoacyl-tRNA is, however, hydrolyzed by the tRNA-specific synthetase. Examples of this are Val-$tRNA^{Ile}$[38,58,59], Thr-$tRNA^{Val}$[38,60], and Ile-$tRNA^{Phe}$[61]. Correction takes place after formation of the enzyme·aminoacyl-tRNA complex and proceeds rapidly as compared with the esterification between the "correct" amino acid and the tRNA[59,60]. A "wrong" newly synthesized ester is presumably cleaved prior to dissociation of the enzyme·aminoacyl·tRNA complex.

The efficiency of proofreading parallels the frequency of mistakes a synthetase makes during the activation of the amino acids. The "correctly" aminoacylated tRNA is also hydrolyzed but much more slowly than the misacylated tRNA. It is not known how the aminoacyl-tRNA synthetase recognizes the amino acid residue of the aminoacyl-tRNA; the amino acid binding site of the synthetase is probably not involved. Misactivated amino acids always have a smaller side chain than the "correct" ones. It is possible that the smaller side chain fits into a hydrolytically active site whereas this is not possible in the case of the "correct" amino acid[44].

The enzymatic hydrolysis of aminoacyl-tRNA is activated by Mg^{2+}. Its dependence does not correspond to the Mg^{2+} dependence of aminoacylation[62]. Sulfhydryl reagents inhibit the hydrolysis in a manner that is different from the inhibition of tRNA aminoacylation[62]. The synthetase probably has a second active center for hydrolysis. The non-esterified hydroxy group in the 2'- or 3'-position of the adenosine residue at the acceptor end of the tRNA appears to be catalytically essential[59,63].

5. Summary and Conclusions

Aminoacyl-tRNA synthetases catalyze the codon-specific esterification of amino acids and transfer ribonucleic acids. The corresponding reactants find each other by normal enzymatic mechanisms, namely as a result of the tightness of the enzyme·substrate complex and of a maximal reaction rate. A feature which is unusual is a correction step catalyzed by the synthetase in which the "wrongly" formed esters are hydrolyzed. This mechanism comes into play if the usual methods for distinguishing between the structurally similar amino acids are not adequate.

The specificity is further improved by the fact that, under physiological conditions, the "correct" amino acid occupies the synthetase in the form of its aminoacyl adenylate and thus minimizes the chance of an association between the enzyme and a "wrong" amino acid. Furthermore, the intracellular concentrations are such as to saturate the synthetases with the "correct" amino acids and tRNAs.

The codon-specific amino acids and transfer ribonucleic acids have high affinities for "their" enzymes. This would, however, result in a catalytically unsuitable saturation of the synthetases with aminoacyl-tRNA if the product did not easily dissociate from the complex. The driving force for the destabilization of the complex is provided at the beginning of the reaction as a result of the fact that the amino acid and ATP occupy energy-rich positions. On transfer of the amino acid residue to the tRNA, the excess energy causes the liberation of the amino acid residue from the active center and thus facilitates dissociation of the synthetase·aminoacyl-tRNA complex.

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Polymeric Catalysts

By Georg Manecke and Winfried Storck[*]

The present-day position in the field of polymeric catalysts is outlined. The following selected groups of polymeric catalysts are discussed: synthetic hydrolases, immobilized enzymes, phase-transfer catalysts, nucleophilically active bases, polymers with conjugated π-systems, photosensitizers, polymers as carriers for catalytically active metals or ions, and immobilized homogeneous catalysts. Polymeric catalysts have the following valuable properties: insoluble polymeric catalysts are readily separable from reaction solutions and can often be re-used without loss of activity; a hydrophobic matrix protects the organometallic active center from deactivation by oxygen and water; by fixation of finely divided metals on an ion exchanger, multistage reactions may be effected successively in one reactor. Polymeric carriers may influence the catalytic properties; for example, in the case of immobilized enzymes on polyionic carriers the pH of the activity maximum may be shifted.

1. Introduction

Attempts have long been made to use polymers as catalysts for chemical reactions, following the prototype of enzymes, the natural polymeric catalysts. Enzymes are characterized by high specificity and high catalytic activity, properties that have also been the goal with synthetic polymeric catalysts. The first advances in this direction were made above all with hydrolytically active polymers: it was observed very early that polymeric acids and polymeric bases, such as occur in ion-exchange resins, can catalyze hydrolytic reactions.

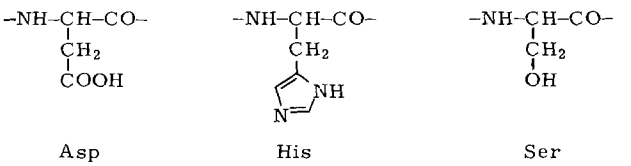
Since then both soluble and insoluble polymeric catalysts have been prepared. The insoluble types have certain practical advantages: they can be separated readily from the substrate and product solutions, they can be used in continuous processes, and they can be simply regenerated and re-used. Valuable metals contained in their active centers can also be easily recovered.

This rapidly expanding field of research has been described in many reviews, often specialized in certain directions. Only a few of these can be cited here[1a–13c], and these without attempting their evaluation.

2. Hydrolytically Active Catalysts

For the sake of a better understanding of the field of synthetic polymeric catalysts we shall first briefly discuss chymotrypsin, probably one of the best investigated enzymes. In proteins and peptides it catalyzes especially the hydrolysis of amide bonds R—CO—NH—R′ whose carbonyl group is derived from an aromatic L-amino acid. X-Ray structure analysis shows that the α-chymotrypsin molecule is ellipsoidal ($51 \times 40 \times 40$ Å^3) and that the active center forms a hydrophobic concavity [(10...12) × (5.5...6.3) × (3.5...4.5) Å^3[14]]. The enzyme-substrate complex appears to be stabilized mainly by an interaction between this hydrophobic reactive grouping and the hydrophobic substrate.

According to *Blow et al.*[15], the functional groups in the side chains of aspartic acid, histidine, and serine in the reactive grouping of α-chymotrypsin are linked by a series of hydrogen bonds.



This association of functional groups is called a "charge relay system". Figure 1 shows the proposed course of amide hydrolysis by chymotrypsin. By means of the "charge relay system" the electrons of the aspartic acid residue ionized at pH 8, lying in the interior of the enzyme, are transferred by way of hydrogen bonds to the serine residue situated on the surface, the nucleophilicity of the latter residue being thus greatly enhanced (Fig. 1a). The hydrolysis itself consists of two partial processes:

In the acylation step the ionized hydroxyl group of the serine attacks the amide-carbonyl group nucleophilically. The enzyme is then acylated and at the same time the amide-nitrogen is protonated. The resulting amine is liberated and the "charge relay system" is broken (Fig. 1b).

In the deacylation step the hydrogen bond system is re-established by the introduction of a water molecule. Under the influence of the ionized aspartic acid the enzyme is deacylated, the carbonyl group is hydroxylated, and the acid is liberated (Fig. 1c).

Since amides and esters were known to be hydrolyzed in the presence of mineral acids, the question whether proteins can be hydrolyzed by ion-exchange resins was already investigated as long ago as in the 1950's. Such reactions were indeed successful[16], and in fact the strongly acidic ion exchangers containing sulfonic acid groups proved to be more active than HCl[17–20]: dipeptides are hydrolyzed about 100 times faster by ion exchangers than by HCl. This can be attributed to bonding of the protonated amino group to the polyanion and to the high proton concentration in the exchanger particles.

A further increase of the catalytic efficiency in ester hydrolysis by cross-linked acids can be achieved by replacing some

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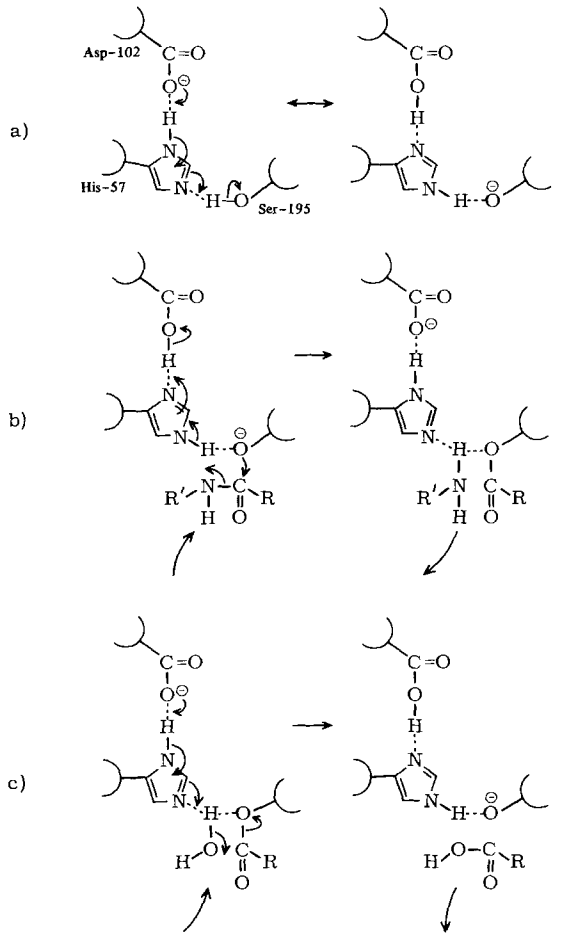


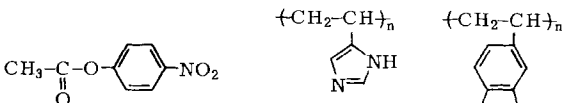
Fig. 1. Postulated mode of action of chymotrypsin. a) "Charge-relay system" at pH 8; b) first step in the hydrolysis of an amide (acylation of the enzyme); c) second step in the hydrolysis (deacylation of the enzyme).

of the protons of the ion-exchanger by cetyltrimethylammonium ions. A more favorable distribution of the hydrophobic substrate follows from the increased hydrophobicity of the polymer[21]. On partial loading with Ag^+ ions the rate of the hydrolysis of allyl acetate can be increased over that of propyl acetate. Apparently the Ag^+ ions form complexes with the allyl group of the ester and thus increase the latter's concentration in the exchanger[22].

The many investigations in this field show that polyacids or polyanions catalyze the hydrolysis of esters, amides, and ethers[23], and indeed often more strongly than mineral acids. The catalytic activity is favored by the higher concentration of protons in the exchanger than in the solution, though this effect is slight. Nevertheless, if the substrate concentration in the polymeric anions is increased by electrostatic and hydrophobic forces of attraction, the catalytic efficiency also increases. Similar results have been reported for hydrolysis by polycations[24–27].

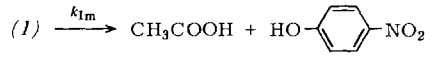
As shown above, the histidine residue in particular is concerned in the catalytic action of hydrolases. Imidazole and its derivatives have therefore been especially studied as catalysts for the hydrolysis of esters. Since the weakly basic imidazole group is unable to remove the much more basic alkoxide ion in a simple ester, most of the investigations were concerned with the catalytic hydrolysis of activated esters such as *p*-nitrophenyl acetate *(1)*.

Overberger[28] was the pioneer in the field of catalytic activity of vinyl polymers containing imidazole groups. His research group synthesized polymers of 4(5)-vinylimidazole and 5(6)-vinylbenzimidazole.



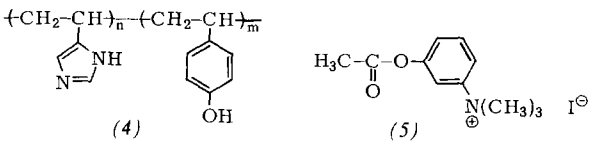
(1) *(2)* PVIm *(3)* PVBIm

The catalytic action of poly[4(5)-vinylimidazole] (PVIm) *(2)* on *(1)* is pH-dependent. Depending on the pH of the medium, the imidazole group may be present in cationic, neutral, or anionic form. In imidazole-catalyzed solvolysis the rate constant k_{Im} depends linearly on the proportion of neutral imidazole. However, the polymer-bound imidazole



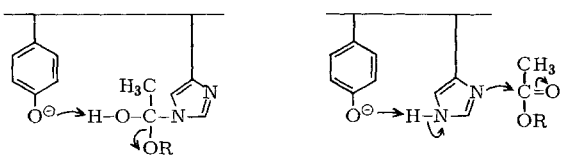
shows an exponential increase in activity with increasing proportion of neutral imidazole, a result explained as due to the cooperative action of two imidazole units[29]. The increased catalytic activity of polymers can also be attributed to attraction of the substrate by secondary forces of attraction. A marked increase in the reaction rate was observed on using long-chain substrates, and this was attributed to increased hydrophobic interaction[30].

The catalytic activity of the imidazole polymers can be considerably influenced by copolymerization. The copolymer *(4)* of 4(5)-imidazole and 4-vinylphenol can be adduced here as example[31]. At high pH a high catalytic activity is found for *(1)*, as also for (3-acetoxyphenyl)trimethylammonium iodide *(5)*. At pH 9.1 the solvolysis of *(5)* in the presence of the polymer *(4)* is 63 times as fast as in the presence of imidazole.



(4) *(5)*

Here there may occur an electrostatic attraction between the cationic substrate *(5)* and the catalyst *(4)*, but the increase in the reaction rate may also be due to a bifunctional attack by the imidazole and the phenolate ion. Imidazole can attack the substrate nucleophilically, while the phenolate ion acts as base on the intermediate (a). The other possibility is a support of the nucleophilic attack by neutral imidazole through the phenolate ion (b).



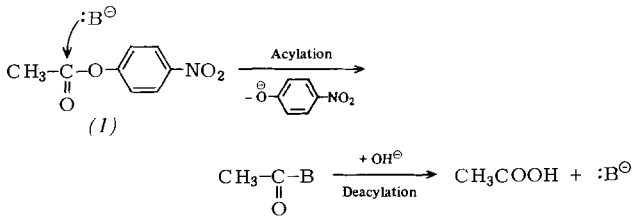
(a) (b)

It could be shown that electrostatic and hydrophobic interactions with the catalytically active grouping caused an

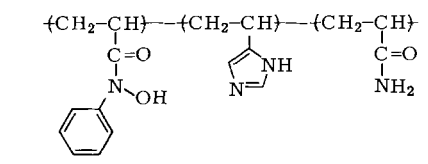
increase in the activity. The chemical structure and the conformation of the polymeric catalyst determine the nature and structure of the catalytic center.

Vinyl polymers with nucleophilic groups other than imidazole can also catalyze hydrolytic reactions; examples are the polymeric hydroxamic acids[32].

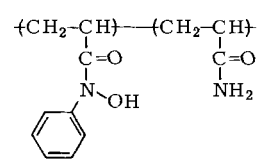
Particular interest attaches to the catalysts prepared by *Kunitake* and *Okahata*[33–35], which contain two nucleophilic groups, for example a hydroxamic acid and imidazole. In the hydrolysis of a *p*-nitrophenyl ester with nucleophilic catalysis by a base an acylated intermediate product is formed, which is deacylated in a second step.



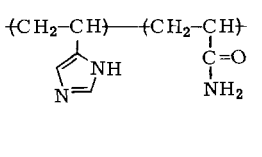
The catalysis is efficient if both the acylation and the deacylation steps occur rapidly. This is difficult to realize if the catalyst contains only one kind of functional group, because a good nucleophile does not usually release the electrophilic partner so easily. An efficient catalyst can be made by combining two functional groups with complementary action: a good nucleophilic group and a second functional group that aids deacylation of the intermediate product. The hydroxamate ion has a high nucleophilicity; deacylation of the acylhydroxamate is a very slow process. To accelerate it, *Kunitake et al.* introduced the imidazole group into the polymer containing the hydroxamic acid. Acrylamide was polymerized in as a hydrophilic component. The polymers *(6)*, *(7)*, and *(8)* were investigated (Table 1).



(6) Poly(PHS-VIm-AAm)



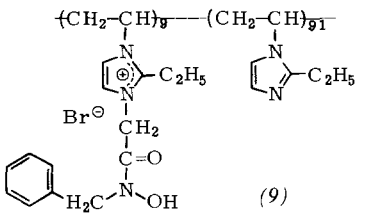
(7) Poly(PHS-AAm)



(8) Poly(VIm-AAm)

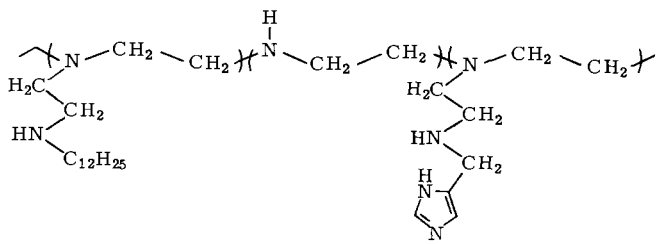
The catalytic activity ($k_{turnover}$) of the bifunctional polymer *(6)* is much greater than that of the monofunctional polymers *(7)* and *(8)*, which contain only the hydroxamic or only the imidazole group. The high catalytic activity of poly(PHA-VIm-AAm) *(6)* is due to the favorable combination of the rate constants k_a and k_d for acylation and deacylation, respectively. k_a is very large for the monofunctional catalyst Poly(PHA-AAm) *(7)*, whereas $k_{turnover}$ is small because of the extremely low k_d. The deacylation rate is increased by a factor of 10^3 by the additional introduction of the imidazole group. The imidazole group can facilitate deacylation in two ways: in general base catalysis it assists attack by water on the intermediate acylhydroxamate; in nucleophilic catalysis transfer of the acyl group of the hydroxamate to the imidazole group results, this reaction being followed by hydrolysis of the acylated imidazole group. The base catalysis appears to predominate.

The nucleophilicity of the hydroxamate ion can be increased by a hydrophobic environment, as has been shown by investigations with cationic polysoaps[37]. Also, hydroxamates that are bound to a cationic poly(vinylimidazole) possess an excellent catalytic activity[38]. An example is the polymer *(9)*.



(9)

As further polymers that catalyze hydrolysis, mention may be made of the poly(ethylenimine) derivatives. Distinct catalytic activity is found in poly(ethylenimine), which is produced by ring-opening polymerization of ethylenimine (aziridine)



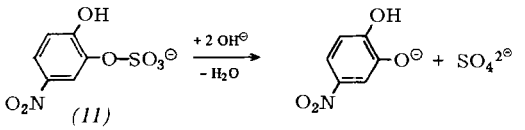
Mol-% 10 15 *(10)*

Table 1. Rate constants for bifunctional *(6)* and monofunctional polymeric catalysts *(7)*, *(8)* in the hydrolysis of *p*-nitrophenyl acetate *(1)* [35, 36] [a].

Catalyst	Functionality	pH	k_a [b] [l mol^{-1} s^{-1}]	$10^3 \cdot k_d$ [c] [s^{-1}]	$10^5 \cdot k_{turnover}$ [d] [s^{-1}]
(6) Poly(PHS-VIm-AAm) 5 : 35 : 60	bi	8.04	0.79	9.6	7.8
(7) Poly(PHS-AAm) 10 : 90	mono	8.05	1.02	0.0056	0.53
(8) Poly(VIm-AAm) 10 : 90	mono	8.09	0.08	≈1.0	≈0.8

[a] In EtOH/H_2O (28.9 vol.-%), 30°C, $\mu = 0.1$ (KCl), 0.15 M barbital buffer. [b] Rate constants of the acylation. [c] Rate constants of the deacylation. [d] Rate constants for $[(1)]_0 = 10^{-4}$ mol/l since $k_{turnover} = k_a \cdot k_d \cdot [(1)]_0 / (k_a[(1)]_0 + k_a)$.

and has a strongly branched structure with primary amino groups[39]. *Klotz et al.*[40–42] were able to demonstrate that solvolysis of *p*-nitrophenyl esters is considerably accelerated in the presence of lauroyl-substituted poly(ethylenimines). According to *Klotz*, a very high catalytic activity is shown by a poly(ethylenimine) of type *(10)*, whose primary amino groups are completely alkylated by (chloromethyl)imidazole and dodecyl iodide[43–44b]. This polymer has a catalytic activity toward 2-hydroxy-5-nitrophenyl sulfate (4-nitrocatechol sulfate) *(11)* that is 100 times that of type IIA arylsulfatase.



Klotz called this very highly active polymeric catalyst "synzyme" (synthetic enzyme) and explained the high catalytic efficiency as due to the highly branched, compact structure.

Investigations by *Kabanov* and his colleagues[45a,45b] showed that alkyl-substituted poly(ethylenimines) have maximal activity toward *p*-nitrophenyl esters when the catalyst and the substrate contain long alkyl groups.

Since the fully synthetic polymeric catalysts in most cases fail to attain the specificity and the activity of naturally occurring catalysts, *i.e.* enzymes, attempts were made at an early date to prepare semisynthetic catalysts—immobilized enzymes—by combination of an enzyme with a polymeric carrier.

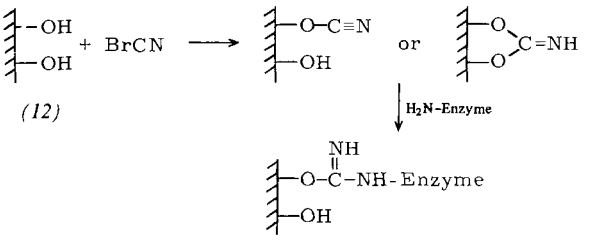
3. Immobilized Enzymes

By treating reactive, insoluble, polymeric carriers with enzymes it proved possible to prepare covalently bonded, insoluble, and immobilized enzymes that retained their biological activity[3,4,46,47]. These immobilized enzymes could be used in studies of metabolic processes. However, they also provide new and interesting possibilities for preparative reactions and for industrial processes. Their especial advantages are their ready separability from the reaction solutions—without this the products are impure—and the possibility of including them in continuous processes. Since they can be re-used, many enzymatic reactions that were previously much too expensive have now become of economic interest.

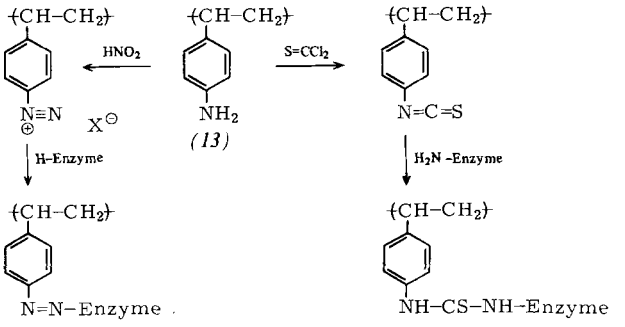
The enzymes can also be immobilized by inclusion in cross-linked gels and by microencapsulation, but immobilization by covalent bonding is for our purposes the most important method[5].

For this purpose insoluble polymers that can swell to a limited extent in water and whose reactive groups can react with the reactive groups of the enzyme are treated with the enzymes under mild reaction conditions. If the bonding does not occur at the biologically active center of the enzyme, the latter's catalytic activity is retained, although usually to a reduced extent.

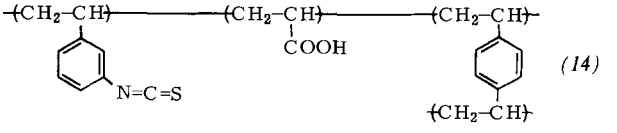
The reactive carriers can be prepared by two methods. The first is the introduction of reactive groups into already known natural or synthetic polymers. For example, cellulose or Sephadex *(12)* is activated by the cyanogen bromide method and then treated with enzymes.



Poly(aminostyrene) *(13)* can be converted into a reactive polymer by diazotization or treatment with thiophosgene. The two fully synthetic polymers also make it possible to immobilize enzymes with retention of their biological activity.



The other principal method of preparing reactive carriers is copolymerization of vinylated compounds that already carry reactive groups, generally with a hydrophilic comonomer and a cross-linking agent. The copolymer *(14)* is presented below as an example.



Many other reactive carrier polymers have been developed. It is now known that it is impossible to prepare a single, generally useful, polymeric reactive carrier. The carrier and the immobilization conditions must be optimized for each enzyme and for each application. Factors other than just the composition of the carrier and the nature of the reactive groups are also responsible for the immobilization reaction and for the properties of the immobilized enzyme. The size of the carrier particles and their specific surface area influence the amount of enzyme bound; in this connection spongy polymers have proved particularly useful. The swelling power of the carrier is also important for the immobilization reaction and for the properties of the immobilized enzyme. The number of reactive groups on the carrier influences the amount of immobilized enzyme. However, there is a limit to the bonding of the enzyme molecules; it is reached when a monomolecular layer has been formed on the accessible inner and outer surfaces of the carrier. If the carrier contains many reactive groups, then the multiple bonding of the enzyme markedly reduces

its catalytic activity. In polyionic carriers the ability to swell is pH-dependent; this also causes the bonding of the enzyme to be pH-dependent. Immobilized enzymes on polyionic carriers generally show a pH shift of their activity maxima; enrichment in the product also often leads to these pH shifts.

In the case of hindered diffusion of the substrate or product in the immobilized enzyme, apparent Michaelis-Menten constants $K_{m(app)}$ are found that are higher than the K_m values of the native enzyme in solution. If, however, the substrate concentration in the immobilized enzyme exceeds that in the external solution, *e.g.* for a polyanionic carrier and a cationic substrate, then $K_{m(app)}$ may be reduced[3].

In some cases immobilized enzymes are more stable to heat than are the native enzymes[48,49]. In the proteases immobilization prevents autodigestion. The activity of some immobilized enzymes does not decrease even on prolonged storage and repeated use[50,51].

Immobilized enzymes offer interesting possibilities for industrial application and for preparative work. Isomerization of glucose to fructose is nowadays probably the most successful industrial process that is effected by immobilized enzymes. It is said that two million tons of isomerized glucose are prepared annually in the United States alone[52,53].

Immobilized lactase is used to cleave lactose to glucose and galactose, and the hydrolyzed lactose finds use as a sweetener for milk products[54].

The hydrolysis of proteins is of special interest to the food industry, as it often improves the taste, solubility, and digestibility of albuminous substances. Thus, casein or soya can be hydrolyzed into free amino acids or into soluble proteins, respectively[55,56]. Fruit juices and wine can be clarified by immobilized pectinase[57]. Large quantities of synthetic DL-amino acids are manufactured; since biological systems utilize only the L-form, it is necessary to separate the racemates. Japanese scientists were the first to separate DL-amino acid mixtures by means of immobilized L-amino acid acylases in a continuous process[58].

As a preliminary step toward semisynthetic penicillin, 6-aminopenicillanic acid is prepared industrially by means of immobilized penicillin amidase[59].

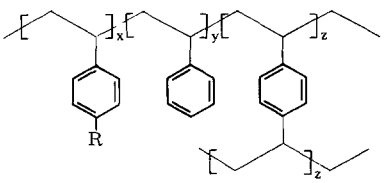
It has further been possible to immobilize complete cells or bacteria that contain suitable enzymes; these retain their activity even on immobilization by inclusion in polymer gels. This process is appreciably cheaper than use of isolated enzymes[60,61]. Thus, fumaric acid has been converted into L-aspartic acid by immobilized cells of *Escherichia coli*. Moreover, several cooperating enzymes may be immobilized in the same matrix[62]. Such immobilized multienzyme systems have much greater overall reaction rates than the corresponding enzymes in a mixture in solution[47], owing to an enrichment of the product of the first enzyme reaction, this being effected in the immediate vicinity of the second immobilized enzyme.

Attempts have also been made to make use of immobilized enzymes in medicine. Encapsulated urease has been used to reduce the blood urea level[63], and L-asparaginase to suppress the growth of L-asparagine-dependent tumors[63]. Immobilized enzymes are also used for analytical purposes[64,65].

Research in the field of immobilized enzymes is in a period of rapid growth, and only a fraction of the results can be mentioned here. Nevertheless, the industrial technology of immobilized enzymes is still in its infancy; polymer chemists have an important part to play in this development, because for each specialized application a tailor-made carrier and an optimized immobilization method are required.

4. Polymeric Phase-transfer Catalysts and Nucleophilically Active Polymers

Systems with onium groups attached to long aliphatic chains can catalyze phase-transfer reactions (catalysis in micelles [66a,66b]). As a result of the action of these catalysts, anions previously added in a high concentration to an aqueous phase are transferred into the organic phase, were they then undergo a nucleophilic exchange reaction with the organic substrate. Loss of the difficultly recoverable, surface-active catalysts can be avoided by anchoring them to polymers. *Brown* and *Jenkins*[67] have prepared polystyrene derivatives of types *(15)* and *(16)*. For nucleophilic displacement of bromide in *n*-octyl bromide by cyanide, the resins *(15)* and *(16)* have the same efficiency as the conventional phase-transfer catalyst tetra-



x = 50...98 z = 2...20
x + y + z = 100

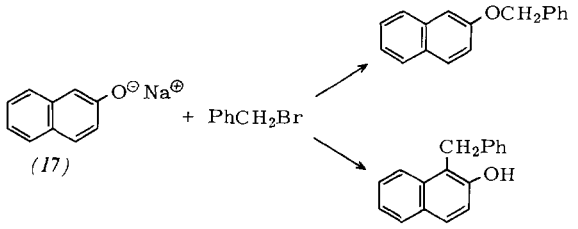
(15), R = $CH_2OCO(CH_2)_{11}\overset{\oplus}{N}(CH_3)_3\ Cl^{\ominus}$
, R = $CH_2OCO(CH_2)_5\overset{\oplus}{N}(CH_3)_3\ Cl^{\ominus}$

n-$C_8H_{17}Br$	+ NaCN	$\xrightarrow{100°C/4\,h}$	n-$C_8H_{17}CN$ + NaBr
2.2 mmol (undiluted or in organic solvent)	>100 mmol (aqueous solution)	10 mol-% catalyst	

butylammonium bromide. According to *Regen*[68,69a], the length of the alkyl chains does not have any great influence on the reaction rate, whereas the latter is drastically affected by the extent of substitution by groups R: if more than 20% of the phenyl groups are substituted, the rate falls to 1/200th of the value found for 10% substitution. *Regen* ascribes this to the fact that slightly substituted polymers swell more strongly in organic solvents, whereas the more heavily substituted polymers have a considerable affinity for water and thus transfer the anions less well into the organic phase. The technique of phase-transfer catalysis with polymeric onium compounds has also been successfully applied to halogen exchange between activated and non-activated halides, to addition of dichlorocarbene to double bonds with the formation of substituted cyclopropanes[69b] and to *C*-alkylation of nitriles[69c]. Optically active polymeric ammonium compounds lead to chiral products when they are used as catalysts in carbene addition reactions[70a,70b].

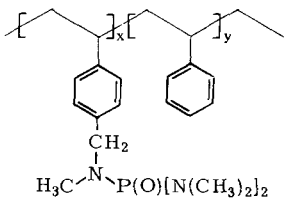
Particular interest attaches to the observation, made by *Brown et al.*[67], that the polymers *(15)* and *(16)* selectively

catalyze *O*-benzylation rather than *C*-alkylation of sodium 2-naphtholate *(17)*: a selectivity of 90% was observed when a molar ratio >0.6:1 of polymer-bound trimethylammonium groups to naphtholate is used.

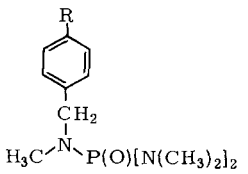


(17)

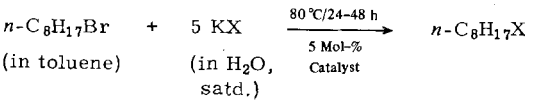
Replacement of the ammonium by a phosphonium group leads to catalysts distinguished by higher thermal and chemical stability[71]. Recently a Japanese group of chemists[72] described the use of polymers of type *(18)* with phosphoramide groups as phase-transfer catalysts for the nucleophilic displacement of bromide by iodide or by acetate. The non-crosslinked polymer was more active than the model compounds of low molecular weight *(19)* and *(20)*; this was ascribed to a cooperative effect of neighboring groups in the polymer during cation formation.



(18), x = 9,5...44
x + y = 100

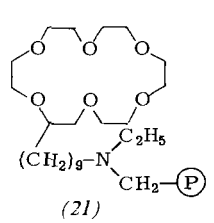


(19), R = H
(20), R = CH=CH2

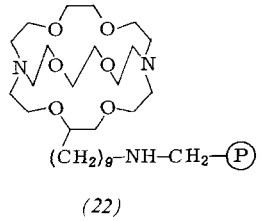


X = I, CH_3COO

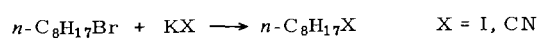
Polymer-bound crown ethers, cryptates, and channel compounds can also be counted among the polymeric phase-transfer catalysts. They catalyze certain reactions on the basis of selective complex formation. *Montanari et al.*[71] studied the nucleophilic replacement of bromine in *n*-octyl bromide by iodide or cyanide in the presence of the oxygen heterocycle [18]-crown-6 *(21)* or the cryptand[222] *(22)*, in each case



(21)

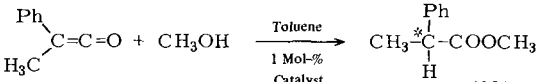


(22)

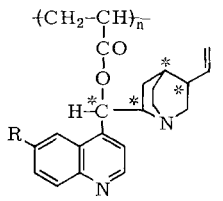


anchored to polystyrene cross-linked with 2% of divinylbenzene. With substitution of ≥2.5 mol-% and the use of 1 mol-% of catalyst, the yields amounted to 95%; these are better than the yields obtained with polymeric onium compounds. The catalytic activity is due to complexing of the cations and the resulting increased nucleophilicity of the anions. The inclusion of a substrate in a channel enables orientation and thus a selective attack: an *O*-alkylated polymer prepared under basic conditions from epichlorohydrin and α-cyclodextrin takes up anisole into its channel; with aqueous hypochlorous acid the anisole can then be converted into *p*-chloroanisole with a specificity of >99%[73]. Poly(acryloyl-β-cyclodextrin) catalyzes the hydrolysis of *p*-nitrophenyl esters more strongly than does free β-cyclodextrin[74].

Addition reactions of H-acidic compounds HX at C=C double bonds in aprotic solvents are catalyzed by tertiary amines. Thus, *Inoue et al.*[75-77] were able to add dodecanethiol to prochiral C=C bonds with optically active poly(*N*-isoalkyl-ethylenimine) as the catalyst, whereby one antipode was formed in slight excess, *i.e.* the reaction product was optically active. The same type of reaction was used by *Yamashita et al.*[78a] when they added methanol to methyl phenyl ketone in the presence of optically active polymeric tertiary amines: the most favorable result was obtained at −78°C in the presence of 1 mol-% of poly(quinine acrylate); a 17% optical yield of the levorotatory methyl (*R*)-2-phenylpropionate *(23)* was obtained, whereas under the same conditions but with poly(cinchonine acrylate) the (*S*)-isomer was formed in an optical yield of 35%[78b].



(23)



R = H: cinchonine
R = OCH_3: quinine

5. Polymeric Catalysts with Conjugated π-Systems

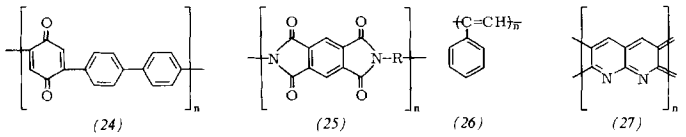
A very different type of chemical structure is involved in those polymers that contain a more or less extensive system of conjugated π-bonds. These polymers catalyze hydrogen-transfer reactions, redox reactions, and—owing to their often considerable concentration of paramagnetic centers—also symmetry-forbidden reactions.

A subsidiary role has hitherto been played in the field of catalysis by oxidation-reduction polymers (redox resins), *i.e.* by polymers that contain isolated (not conjugated) redox systems (mainly quinones) within the polymer chain or as substituent. Sulfide[79] and sulfite[80] solutions can be caused to react with oxygen in the presence of such redox resins containing quinone groups; this reaction has attracted interest in connection with the purification of waste waters.

However, particularly in the sixties, very intensive research was carried out on the properties of polymers that contain an extensive system of conjugated π-bonds. In Table 2 are collected some examples of these polymers and the reactions catalyzed by them. According to *Manassen*[9], it is in most cases possible to understand the mechanism of the catalysis

by recalling the reaction schemes obtained for low-molecular models.

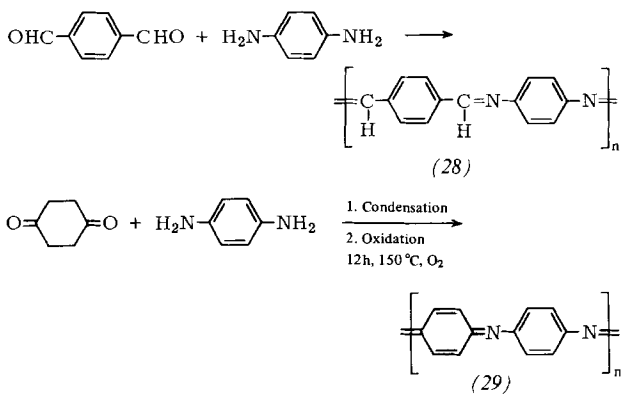
Table 2. Polymers containing extended systems of π-bonds and reactions catalyzed by them.



(24) (25) (26) (27)

Polymer	Dehydrogenation (in the presence of O_2)	Dehydration	Isomerization	H_2O_2	Decomp of: HCOOH	Decomp of: N_2O	Reaction p-$H_2 \rightarrow o$-H_2	Exchange $H \rightarrow D$
(24) Poly(arylenebenzoquinone)	[81, 82]							
(25) Poly(pyromellitimide) [83, 84]	none [85]	none [85]	none [85]		[86a]	[83–86a]		
(26) Poly(phenylacetylene) [87, 88]		[88, 89]	[87]					
Pyro[poly(*p*-diethynylbenzene)] [90]					[90]		[90]	[90]
(27) Pyro[poly(acrylonitrile)]	[85, 86a, 91]	[85, 86a, 92]	[85, 86a, 91, 96]	[93, 94]	[95]	[85, 86a, 97, 98]		

Summarizing the available extensive experimental material, it appears that dehydrogenations are catalyzed by polymers only if they contain a quinonoid structure. *Manassen*[96a] demonstrated this strikingly for the two linear and polyconjugated condensation products *(28)* and *(29)*. Only the product *(29)*, having a quinonoid structure, catalyzed the dehydrogenation of cyclohexane to benzene, while compound *(28)* was totally inactive. Further investigations of Schiff bases of type *(29)* have been carried out by *Uehara*[96b]. A similar high selectivity was found by *Iwasawa et al.*[99a] with poly(naphthoquinone): ethylbenzene was dehydrogenated exclusively to styrene, and cyclohexanol yielded 98% of cyclohexanone and 2% of cyclohexane; hydrogen sulfide was dehydrogenated to sulfur[99b]. However, pyropolymers also exert a dehydrogenating effect: since, however, these have been subjected without exception to often drastic thermal treatment in the presence of oxygen, the formation of acidic functions must be taken into account. This can be recognized in the ability to dehydrate alcohols and to catalyze isomerizations; as an example only pyrolyzed poly(acrylonitrile) *(27)* will be mentioned here (cf. Table 2).



(28) (29)

The extended π-systems in the polymers considered here influence their physicochemical properties. Thus, the high concentration of delocalized electrons along the conjugated chain that also often contains hetero atoms and in many cases is cross-linked two- or three-dimensionally leads to the following three phenomena: 1. a high content of free spin; 2. a decrease in the internal energy of the system; 3. a lowering of the triplet excitation energy. These give rise to the paramagnetic behavior, the good thermal stability, and the semiconductor properties of the polymers.

Although it had often been assumed that there is a direct relation between the catalytic activity and electrical conductivity, this could be confirmed directly only for series of polymers of the same type and very similar chemical structure[100]. Since, however, a high proportion of the polymers examined have semiconductor properties, it follows that conductivity is a necessary but not sufficient prerequisite for catalytic activity. An appreciably more precise relationship has been found between the concentration of free spin and some decomposition and rearrangement reactions that are themselves symmetry-forbidden. In particular, *Gallard*'s school[83, 85, 86a–c] succeeded in establishing relationships between the magnetic properties of organic polymers and the symmetry-forbidden

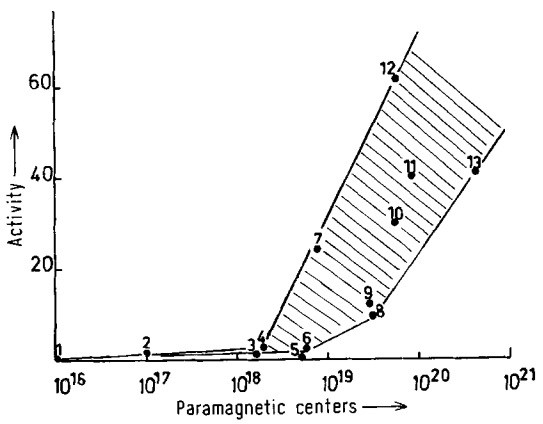


Fig. 2. Correlation between the catalytic activity for the decomposition of dinitrogen oxide

$N_2O \rightarrow N_2 + {}^1/_2 O_2$

and the logarithm of the concentration of paramagnetic centers in the catalyst [83]. 1) Melon; 2) terephthalaldehyde-benzidine polycondensate; 3) tetrachloro-*p*-benzoquinone-benzidine polycondensate; 4) poly(quinoxaline) 1; 5) poly(diphenyldiacetylene); 6) poly(quinoxaline) 2; 7) poly(acrylonitrile), pyrolyzed at 250 °C; 8) Aniline Black; 9) Paramine Brown; 10) poly(benzimidazole); 11) poly(isoprene), treated with tetrachloro-*p*-benzoquinone; 12) poly(acrylonitrile), pyrolyzed at 350 °C; 13) poly(isoprene), treated with *p*-benzoquinone. The activity is measured in arbitrary units with respect to 1 m^2 of surface area of the catalyst [86a–c].

decomposition of dinitrogen oxide catalyzed by them. As an example reference can be made to the very extensive investigations into the correlation of catalytic activity and concentration of free spin (Fig. 2)[83]. Below a concentration of $10^{18.5}$ spins/g none of the thirteen polymers studied had a marked catalytic activity, whereas at higher spin concentrations the active polymers, which have widely differing structures, occupy a relatively narrow field in Figure 2. The relationship thus presumed between the effective length of the unbroken system of conjugated π-bonds in the polymer chain and the catalytic activity of the paramagnetic centers has been confirmed by measurements on a series of structurally different poly(pyromellitimides) and poly(indoloimidazoles)[83].

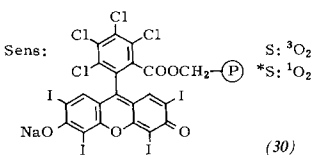
6. Polymer-bound Photosensitizers

A different kind of catalysis is involved in the excitation of molecules into the excited state: a sensitizer (Sens), generally a dyestuff, is excited by light energy *hv* to the singlet state, passes without emitting radiation into a longer-lived triplet state, and can then activate a substrate molecule (S), itself returning to the ground state:

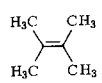
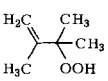
$$\text{Sens} \rightarrow {}^*\text{Sens} \rightarrow {}^3\text{Sens}$$
$${}^3\text{Sens} + \text{S} \rightarrow {}^*\text{S} + \text{Sens}$$

Neckers et al.[101a] bonded the sensitizer Rose Bengal in ester fashion to cross-linked poly(styrene) and used this for the production of singlet oxygen; the latter at once reacted with oxidation with suitable acceptors. Table 3 shows that

Table 3. Oxidation with photochemically produced singlet oxygen $^1O_2$ [101a]. Sensitizer: Rose Bengal *(30)*, bound to poly(styrene) Ⓟ cross-linked with divinylbenzene.



(30)

$^1O_2$ acceptor	Product	Yield [%]
		95
		69
		82

the reactions proceed in high yield; the sensitizer can be simply filtered off from the solution and re-used.

For potential use in solar energy storage the conversion of norbornadiene to quadricyclene by sun light in the presence of various polymeric sensitizers is under study[101b].

7. Polymeric Organic Catalysts Containing Metals

In this section we shall consider polymeric organic catalysts containing metals. These will be divided into two groups: in the first group the catalytic centers contain free metal, in the second the metal is bound to the polymer in the form of an ion, a complex, or a chelate. Coordination polymers are not considered in this connection.

7.1. Catalysts Containing Free Metal

At first sight the group of polymers containing free metal appears to correspond to the heterogeneous catalysts on inorganic carriers—a group used widely in industry—but with the difference that the carrier is a polymer. Here already the analogy breaks down, because organic polymers can assume varied chemical or physical forms and be suited to a specific purpose. For example, metal particles with a mean diameter of about 15 nm can be produced in a polymer gel: a metal salt solution is equilibrated with a neutral, slightly cross-linked gel of poly(2-hydroxyethyl methacrylate) and then reduced with sodium tetrahydridoborate. Since the swelling capacity of the gel varies according to the solvent, the selectivity can be controlled by diffusion for these nonpyrophoric, readily separable, and re-usable catalysts. This has been demonstrated, among other cases, for the hydrogenation of cinnamaldehyde, mainly to hydrocinnamaldehyde, in the presence of a Pd-containing gel; the selectivity is higher than with a conventional Pd/C catalyst[102]. On the other hand, PtO_2, Ni, or Rh particles can also be microencapsulated by cross-linking interfacial polycondensation; if ferromagnetic material is added to the batch, then after hydrogenation the capsules can be easily separated from the batch by a magnetic field[103]. As a third possibility, the catalyst particles may be dispersed in solid polymers that can then be processed into some form, *e.g.* film, that is advantageous for a technical process[104].

It has long been known for inorganic heterogeneous catalysts that the carrier influences the catalytically active material dispersed on it. A similar effect was therefore suspected for polymeric carriers. *Rase et al.*[105] confirmed this in their study of the catalytic activity of Pt deposited on chemically different polyamides for the hydrogenation of benzene to cyclohexane. Only considerably later were the differences found to be due to Pt complexes formed in the preparation, which contained the N atoms of two amide groups[106a, 106b]. *Beamer et al.*[107] precipitated Pd on optically active poly(amino acids) and used the product as a hydrogenation catalyst for prochiral C=C bonds. A close relationship was found between the tertiary structure of the support and the observed direction of optical activation.

An elegant method of depositing finely divided metals on or within polymers consists of the use of ion exchangers and ion-exchanging polymers. In this one can rely either on the mechanical and geometric properties—in the micro or macro region—of these well investigated polymers, or on the fact that the separately bound ion-exchange groups lead to an extremely homogeneous distribution of the metal ions or metal complexes. In a subsequent reducing process, *e.g.* with hydrazine or by a process not involving additional reagents, the metal is deposited in the form of extremely small particles with a diameter of ≤ 2 nm and high catalytic activity. Some examples are presented in Table 4. Special reference should be made to a series of papers by *Germain et al.*[114–118], whose results can be summarized as follows: the metal is precipitated in a highly disperse form in the exchanger, vari-

Table 4. Metal-charged ion exchangers as catalysts.

Ion exchanger	Type [a]	Charged with	Activation	Process catalyzed	Ref.
Amberlyst 15	C; m; s.a.	$Pd(NH_3)_4Cl_2$	NH_2NH_2	Hydrogenation	[108]
Amberlite A21	A; m; w.b.	K_2PdCl_4	NH_2NH_2	Hydrogenation	[108]
Amberlite A21	A; m; w.b.	$RhCl_3 \cdot 3H_2O$	—	Hydrogenation	[108—110]
				Shift of double bond	
Amberlyst A27	A; m; s.b.	$RhCl_3 \cdot 3H_2O$	H_2	Hydrogenation	[111]
IRC 84	C; —; w.a.	$RhCl_3 \cdot 3H_2O$	—	Hydrogenation	[112a, 112b]
Chelex 100	C; —; w.a.	$PdCl_2$	—	Selective hydrogenation	[112c]
				of conjugated double bonds	[113a]
Amberlyst 15	C; m; s.a.	$Pt(NH_3)_4Cl_2$	NH_2NH_2	Hydration + dehydrogenation	[113b]
Cation exchanger	C; m; s.a.	$AlCl_3$	—	Paraffin isomerization and cracking	
Amberlyst 15	C; m; s.a.	$Pt(1,5\text{-cod})_2Cl_2$	—	Acetalization + dehydration + hydrogenation	[110]

[a] C = cation exchanger; A = anion exchanger; m = macroporous; s = strong; w = weak; a = acid; b = basic.

ously active or selective zones being formed; the activity, calculated on the weight of the metal, is considerably higher than in conventional active-charcoal carriers; the selectivity for partial hydrogenation of triple bonds with Pd catalysts is good, and a certain selectivity for space-filling substituted substrates can be demonstrated. Particular attention should be paid to the possibility of catalyzing several reactions with the ion-exchanger/metal system, as shown in the following sequence[110]:

$$CH_3OH + CH_3COCH_3 \longrightarrow \left[\begin{array}{l} HO \quad OCH_3 \\ CH_3\text{–}C\text{–}CH_3 \end{array}\right] \xrightarrow[-H_2O]{}$$

$$\begin{array}{l} OCH_3 \\ CH_2{=}C{-}CH_3 \end{array} \xrightarrow{H_2} \begin{array}{l} OCH_3 \\ CH_3{-}CH{-}CH_3 \end{array}$$

The catalyst used for this sequence was a macroporous, strongly acidic cation exchanger charged with the complex $Pt(1,5\text{-cyclooctadiene})_2Cl_2$.

7.2. Catalysts Containing the Metal in the Form of a Compound, Ion, or Complex

Polymers in general, but particularly ion exchangers and polymers with ligands that form complexes or chelates, are also well suited as carriers for catalytically active metal compounds. Some examples have been collected in Table 5. The advantages of these catalysts are again that they can be easily separated and re-used. Additionally, for an immobilized complex in a rigid system there is no saturation concentration

$$CH_2{=}CH{-}CH_2Cl + CO \xrightarrow[68.9\ bar]{100\ ^\circ C} CH_2{=}CH{-}CH_2COCl \rightleftharpoons CH_3{-}CH{=}CH{-}COCl$$

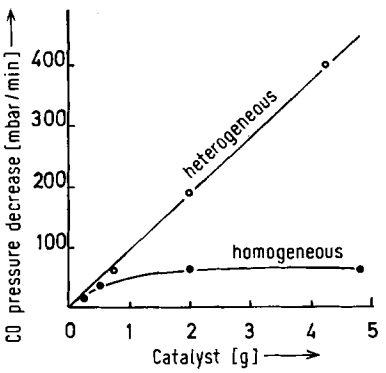


Fig. 3. Homogeneously and heterogeneously catalyzed carbonylation of allyl chloride. Homogeneous catalysis with $[Pd^{II}(NH_3)_4][p\text{-}CH_3C_6H_4SO_3]_2$; heterogeneous catalysis with polystyrenesulfonic acid exchanger charged with $[Pd^{II}(NH_3)_4]^{2+}$ [132].

Table 5. Polymers charged with metal complexes as catalysts.

Polymer	Metal complex or ion	Process catalyzed	Ref.
Poly(styrene)	$AlCl_3$	Etherification of acid-sensitive alcohols	[119]
	$Mo(CO)_3$	Friedel-Crafts reaction; selective with regard to *p*-substitution	[120]
Cation exchanger	Hg^{2+}	Hydration of —C≡C— bonds	[121a—121c]
		Transvinylation	[122a, 122b]
	Mn^{2+}, Co^{2+}, Ni^{2+}	Oxidation of cyclohexane to cyclohexanone	[123]
	$VO^{2+} + Na^+$	Epoxidation of cyclohexene	[124a]
Anion exchanger	Mo oxalate	Hydration of olefins	[125]
	HWO_4^-	Epoxidation of maleic acid with H_2O_2	[126a, 126b]
	Pt^{4+}, Pt^{2+}	Hydrosilylation of olefinic double bonds	[127a, 127b]
	$[Rh_2Cl_9]^-$	Hydrosilylation of olefinic double bonds	[127c]
	$Mo(CO)_6$	Epoxidation of propene	[124b]
	$[Mo_2O_4(ox)_2(H_2O)_2]^{2-}$	Epoxidation of cyclohexene	[124c]
Poly(acrylonitrile)	Cu^{2+}, La^{3+}	Oxidation of cumene to cumyl hydroperoxide	[128]
Poly[pyro(acrylonitrile)]	Ag^+	Oxidation of ethylene to ethylene oxide	[129a]
Poly(2,2'-disulfobiphenylene benzoquinone)	Pd^{2+}	Oxidation of ethylene to acetaldehyde	[129b]
Poly(vinylpyridine)	VO^{2+}	Epoxidation of cyclohexene	[124d]
	Ni^{2+}, Co^{2+}	Oligomerization of olefins	[130a]
	$RhCl(CO)_2$; $RuCl_2(CO)_3$	Isomerization of 1-butene	[130b]
	Cu^{2+}/Cu^+	Oxidative polymerization of dimethylphenol	[131a]
	Cu^{2+}/Cu^+	$2ROH + CO + \frac{1}{2}O_2 \rightarrow OC(OR)_2 + H_2O$	[131b]

and no inactivation by dimerization or polymer formation. *Haag* and *Whitehurst*[132] investigated the carbonylation of allyl chloride in the presence of Pd complexes (Fig. 3). While an initially completely soluble, low-molecular (homogeneous) catalyst with increasing concentration reaches saturation and thus an activity independent of the amount present, for a high-molecular catalyst—a strongly acid cation exchanger charged with $Pd(NH_3)_4^{2+}$—a linear relationship is found between its activity and its amount over a wide region. Saturation phenomena are thus avoided and in such cases an increased rate of conversion is attained.

This example shows very clearly the advantages that can be gained by immobilization—also called heterogenation—of catalysts that alone are highly active only in the homogeneous phase. If we recall that at present about 20 industrial processes are carried out with homogeneous catalysts[133], *e.g.* the hydrogenation of olefins, hydroformylation of olefins to aldehydes, carbonylation of alcohols to acids, oxidation of olefins to aldehydes, ketones, and vinyl esters, in addition to many polymerizations, we can recognize the importance afforded by such an advance in industrial practice. Since the end of the 1960's intensive efforts have therefore been devoted to the immobilization of homogeneous catalysts.

Homogeneous catalysts are clearly defined substances that can be prepared with a high degree of reproducibility. Since the steric and electronic environment of the catalytic centers in homogeneous catalysts can be varied within wide limits, the selectivity and the reaction rate can be controlled. This in no way applies to heterogeneous catalysts, which are therefore difficult to develop further. In addition, in the latter only a small proportion of the active centers are accessible and hence effective, whereas in the homogeneous phase in principle all active molecules take part in the course of the reaction. Furthermore, homogeneously catalyzed reactions can often be carried out under milder conditions and have better mass and temperature characteristics. Alongside these clear advantages of homogeneous catalysts, however, some problems that arise in industrial application must also be mentioned. In the first place, some of these noble-metal complexes have a corrosive action on the reactors, leading to deposition of metal on the reactor walls; this results in a loss of catalyst and in formation of new active centers with undesirable properties. Apart from the difficulty in realizing a continuous mode of the reaction, however, the main disadvantage is the difficulty of the catalyst's recovery. According to the nature of the catalyst and the product, this often necessitates a repetition of expensive separations. Moreover, in many cases the active catalyst cannot be recovered as such, but only a portion of the noble metal.

Many processes have been proposed for separation and recovery. *Manassen*[134] attempted to solve the problem by means of a homogeneous catalyst that was only slightly altered chemically by reaction in two immiscible liquid phases: one phase contained the catalyst, the other the substrate and the product. The first experiments have been encouraging, but in principle the possible applications are severely limited. *Bayer* and *Schurig*[135] also worked with a homogeneous phase; these authors bound homogeneous catalysts by ligand exchange to soluble poly(styrene) functionalized with phosphane groups; the polymeric catalyst isolated by membrane filtration was re-used successfully and repeatedly.

Industrial and academic activity is now concentrated on chemical fixation of known active homogeneous catalysts onto organic cross-linked polymers and, very recently, also onto inorganic carriers[136a–136c].

At present the great majority of polymers suitable for immobilization of homogeneous catalysts use arylphosphane groups, and are prepared almost exclusively by polymer-analogous reactions. The steps outlined in Figure 4 have proved useful for poly(styrene)[137].

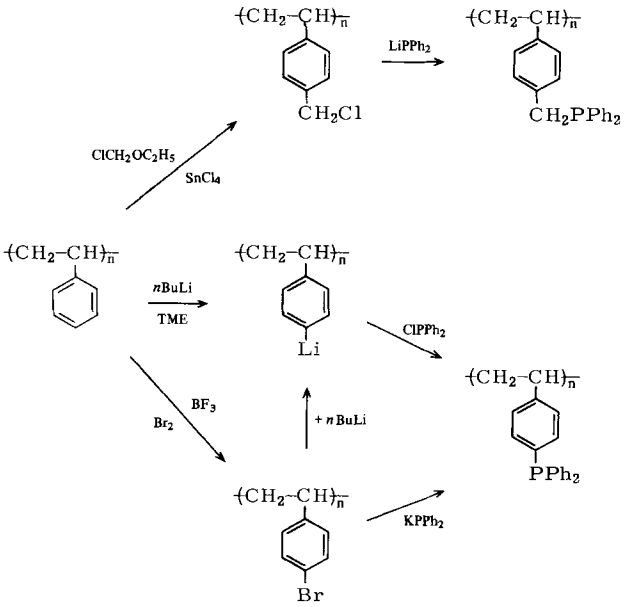


Fig. 4. Polymer-analogous reactions with poly(styrene) (homopolymerizate or bead polymerizate cross-linked with divinylbenzene) for the introduction of phosphane groups [137]. TME = tetramethylethylenediamine.

The catalyst itself is obtained in a further step by ligand exchange with a homogeneous catalyst; this is illustrated for the Wilkinson catalyst *(31)*.

$$\text{Ⓟ—PPh}_2 + \text{ClRh(PPh}_3)_3 \longrightarrow \left[\text{Ⓟ—PPh}_2\right]_x \text{RhCl(PPh}_3)_{3-x}$$

(31), $x \geq 1$

Special treatment is often necessary to endow the bound metal complex with catalytic activity. A prerequisite for catalytic activity is the presence of a free coordination site on the metal[138].

The test reaction generally used is hydrogenation, but hydrosilylations[139a, 139b], hydroformylations[140–142b], carbonylation of methanol[143a, 143b], isomerizations[144], oligomerizations, and cyclooligomerizations[145a, 146b] have so far also been studied with these new catalysts. In this work considerable differences in the product distribution have sometimes been observed in comparisons with the results for pure homogeneous catalysts.

In spite of their apparent simplicity, immobilized homogeneous catalysts present a very complicated picture. In many cases even the structure of the bound complex is unclear. While the properties of active metal complexes fixed on soluble polymers in the homogeneous phase are only slightly altered by the immobilization process, such alterations are considerable for catalysts bound to cross-linked polymers swelling only to a limited extent. The customary comparison with a homogeneous catalyst on the basis of the reaction rates

and the product distribution rarely indicates more than that a difference exists; hitherto it has not been possible to establish the reaction kinetics on a theoretical, quantitative basis.

For example, the catalytic process is influenced by the following factors: particle size of the polymer, distribution of the catalyst in the particles, percentage porosity, pore size, and pore structure under the reaction conditions, number of ligands on the polymer (multiple coordination), rigidity of the polymer (extent of cross-linking), and the influence exerted on the swelling behavior of the catalyst by the substrate, product, and solvent. It is difficult to establish how on the one hand the chemical structure of the catalytic centers and on the other the rates of diffusion of the substrate and product are influenced by these factors. It is therefore not surprising that the observed effects have many causes. For example, it is frequently found that the reaction rate is retarded by the size and branching of the substrate, as shown in Table 6 for hydrogenation with an immobilized Wilkinson catalyst[147]. The high selectivity observed here is certainly due to a combination of several parameters determining diffusion.

Table 6. Relative rates of hydrogenation of olefins in the presence of rhodium catalysts [147]. Hydrogenation conditions: 1 M olefin solution in benzene, 25°C, 1013 mbar. Catalyst I: [Ⓟ PPh_2]$_x$RhCl$(PPh_3)_{3-x}$:Ⓟ: chloromethylated styrene bead polymerizate cross-linked with 1.8% of divinylbenzene, ϕ 15—35 μm; 0.13 mmol Rh/g dry polymer. Catalyst II: $ClRh(PPh_3)_3$, 2.5 mmol.

Olefin	Cat. I	Cat. II
1-Hexene	2.55	1.4
Cyclohexene	1.00	1.00
Octadecene (isomer mixture)	1/2.06	1/1.4
Cyclooctene	1/2.54	1.0
Cyclodecene (*cis* and *trans*)	1/4.45	1/1.15
2-Cholestene	1/32	1/1.4

The absolute rate of hydrogenation with the heterogeneous catalyst is 1/6 of that for the homogeneous catalyst; in contrast, the rate was observed to be increased by a factor of 25 with immobilized titanocene[148,149] (Table 7). The presumed explanation was that deactivation by dimerization and polymerization was hindered by fixation of the titanium complex on the very rigid matrix.

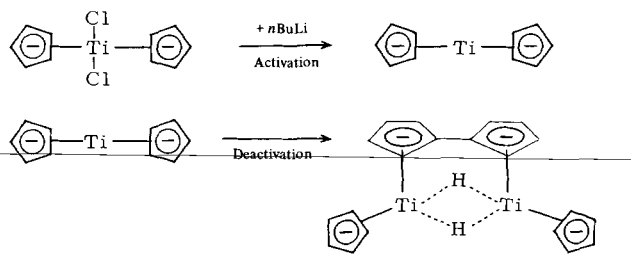
Table 7. Hydrogenation of cyclohexene with titanocene catalysts. Hydrogenation conditions: 1.16 M cyclohexene solution in *n*-hexane, 20°C, 1013 mbar [148].

	v [ml H_2/(min·meq·Ti)]	$\frac{v_{heterogen.}}{v_{homogen.}}$
Homogeneous catalyst	28.0	—
Immobilized catalyst [a]	88.7	3.2
Immobilized catalyst, milled	714	25.5

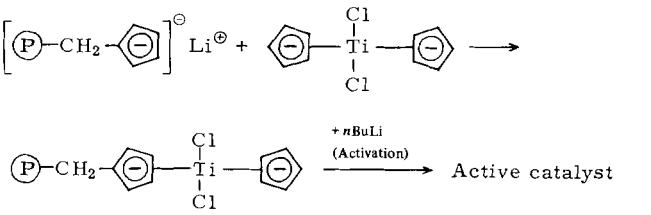
[a] Titanocene bound on macroporous styrene bead polymerizate cross-linked with 20% of divinylbenzene; 0.28 meq·Ti/g.

A very far-reaching influence of the matrix was observed by *Kagan et al.*[150] on using a chiral ligand (Table 8). When poly(styrene) cross-linked with 2% of divinylbenzene was used as the carrier for the rhodium complex, hydrogenation was possible only in benzene and the optical yields were only

Monomeric titanocene catalyst

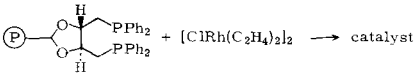


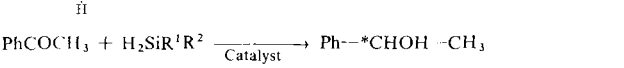
Polymeric titanocene catalyst



$^1/_{10}$th of the yields found with the low-molecular homogeneous catalyst. The catalyst is unsuitable for reactions in polar solvents: *e.g.* it shrank very strongly in ethanol with loss of activity. When a dihydrosilane was used as the source of

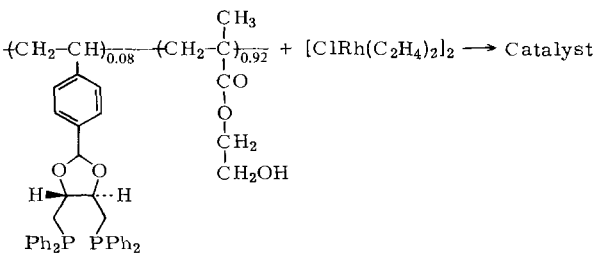
Table 8. Reduction of acetophenone by dihydrosilane in the presence of a polymeric chiral rhodium catalyst. Ⓟ = poly(styrene) cross-linked with 2% of divinylbenzene [150].

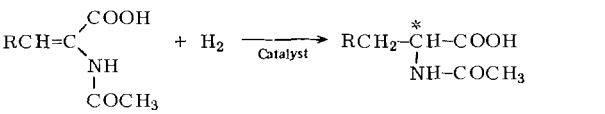




R^1	R^2	Opt. yield [%]
CH_3	Ph	8
Ph	Ph	29
Ph	1-Naphthyl	52

hydrogen, acetophenone could be reduced to 1-phenylethanol in high chemical and optical yields. The optical yield was then just as large as with the low-molecular model and in both cases increased with increasing rigidity of the silane substituents. For the use of this effective chiral catalyst in polar solvents the polymeric carrier was changed by *Stille et al.*[151a,151b]: the copolymer from 2-*p*-styryl-4,5-bis(tosyloxymethyl)-1,3-dioxolane, 2-hydroxyethyl methacrylate





(32), R = Ph
(33), R = H

(34), 86% opt. yield
(35), 52-60% opt. yield

and a small amount of ethylene dimethacrylate gave, after phosphonation with sodium diphenylphosphide, a matrix that could swell well in polar solvents. α-Acetamidocinnamic acid *(32)* and α-acetamidoacrylic acid *(33)* were hydrogenated in ethanol with the resulting polar, chiral, heterogeneous rhodium catalyst. The optical yields of *(34)* and *(35)* were similar to those obtained in experiments with the low-molecular homogeneous catalyst. The heterogeneous catalyst could be re-used, but it was more sensitive to oxygen than the analogous catalyst based on poly(styrene).

Summarizing, it can be stated that there are very many gaps in our knowledge of immobilized homogeneous catalysts and that no more than a start has been made with a systematic investigation of their properties. The work to date has shown, however, that these new catalysts have valuable properties: they are easily separated and can be re-used without loss of activity; an alteration of their porosity leads to an altered selectivity[152]; the hydrophobic matrix that is often favored protects the active centers from deactivation by oxygen and water[119, 153]; by fixation of two or more catalysts on one carrier multistage reactions can be carried out successively in one reactor[143b, 154], on occasions indeed in conjunction with one another; fixation of the active centers on a rigid matrix prevents their deactivating reaction with one another[148, 149]; and the use of chiral ligands makes it possible to synthesize optically active compounds[150–151b]. This list of favorable properties will certainly be extended in the future.

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The Responsibility of the Scientist[**]

By Hans Mohr[*]

The tradition of mutual trust between science and the public appears to have been broken in recent years. It is necessary to define the boundaries of science and to reflect upon the responsibility of the scientist.

The goal of science is knowledge.

Just a few years ago most scientists were full of confidence, and science was an unquestionable component of our culture. Any increase of knowledge was considered almost synonymous with moral progress, with more humanitarianism, more freedom, more happiness. The scientist expected the public to respect his work and to trust him. In most cases, this trust was granted *blindly*.

All that has now changed. Science as an institution and the scientist as a person have been drawn into the general crisis of confidence which has pervaded society. Science and the technology to which it gave birth are now largely regarded as *enemies* of mankind. The critics maintain that science has disappointed, and in particular that it has failed *morally*.

Has science really failed?

At first glance it would not appear to be the case. On the contrary: modern science was, and still is, remarkably effective. Advances in knowledge continue, in some disciplines at an unprecedented rate. We all live from the fruits of science; and we live better, far better, than mankind has ever lived before. Anybody who denies this does not know (or does not want to know) how our ancestors lived and suffered. Of course, the point of no return has long been passed. There are simply 3 or 4 billion people too many for any return to the *simple* way of life, even if it were desirable. If we wish to continue to live we must therefore overcompensate the decay phenomena of our culture by scientific and technological progress. If distrust of *Homo faber* were to lead man to turn his back on science, this would be his farewell to civilization.

Nor would science appear to have failed *morally*. The ethos of science, that particular moral law which provides the basis for objective knowledge, has stood the test better than any other set of norms and values in the history of man. There is not the slightest indication that science has lost any of its rigor in the classical disciplines. On the contrary, the severity of sanctions imposed upon those deviating from this ethos has increased.

How, then, did the accusation arise that science has failed? I think it is because mankind expects more from science than it can afford according to its goal and structure. Serious scientists, experts in their respective fields, were also guilty in the 1960's of cultivating the illusion that any problem is solvable if we really desire its solution; they promised not only knowledge and explanation, but also salvation. Science is now criticized as an institution because these promises cannot be fulfilled. It was partly the fantastic successes of those years, such as the first moon landing or the breaking of the genetic code, which deluded scientists into making such promises. The principal reason, however, lay (and still lies) in the inability of many scientists to distinguish between those problems which are *directly* accessible to a scientific or technological solution and those whose solution requires a change in the prevailing propensity structure or in the *system of values* of society. The latter problems cause the real difficulties because there are narrow limits set to the changes in values and the structure of natural tendencies.

It was a lack of insight into the nature and structure of problems which led to the overoptimistic view that a global attack by the elite of science could also solve the world's greatest problems: overpopulation, need and poverty, exhaustion of reserves, destruction of the environment, chauvinism, collective envy, economic extortion, ideological fanaticism.

Given clearly defined and simple aims and constant scales of values in society, the capability of science is almost without limit. If the aim is vague and attainable only after modification of the prevailing scale of values or the prevailing propensity structure of human society, then science proves inadequate or, far worse, partial scientific solutions (such as the "green revolution" in the fight against hunger) only *exacerbate* the overall problem.

At this juncture I must delineate the term *science* to avoid any future misunderstanding. The aim of science is knowledge;

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knowledge of the kind which provides a reliable basis for dealing with the real world (including people) and for dealing with ideas. Knowledge is expressed in the form of propositions. General propositions are called laws, while singular propositions are termed facts. The distinguishing feature of science, as compared with all other activities of the mind, is the existence of strict methods to examine whether a proposition is true or false.

The "scientific ethos" is a coherent and surprisingly consistent code of rules and regulations embracing the following requirements: primacy of knowledge (knowledge is better than ignorance in all circumstances), intellectual honesty, mutual respect, objectivity, freedom of thought (and hence renunciation of any rejection of information), symmetrical argumentation, clarity of expression. It is of particular importance that scientific statements should be testable without restriction at all times. A statement is permissible only if its correctness can be checked by anybody who is mentally and technically equipped to do so.

This code is strictly applied by the scientific community. Anybody who employs inadequately defined concepts, who reports false data, who makes careless statements, who operates with theories that cannot be subjected to empirical scrutiny, or who purposely tries to discredit others will lose his trustworthiness and the respect of his colleagues, and will sooner or later leave the sphere of science.

Of course, *unintentionally* false measurement, reasoning, and argumentation represent an unavoidable and ever-present danger threatening the advancement of knowledge. It is therefore all the more important that we do not have to consider *intentionally* false measurement, reasoning, and argumentation.

The scientific ethos is shown by its success to be an extremely powerful principle. However, and this limitation is of crucial importance, it is a *partial* ethos which imposes ethical standards on us solely with regard to a given end. This end is knowledge. As long as a person's actions have the aim of furthering scientific knowledge, he subjects himself to the scientific ethos. In the fields of human relationships, economics, or politics no binding maxims are forthcoming from the scientific ethos. It is a partial ethos which, moreover, only partially rules the life of the scientist. In their *personal* lives, and sometimes in their personal dealings with one another, scientists are neither particularly "noble", nor particularly "helpful", nor particularly "good". Why should they be? Their qualification and their status as *scientists* are independent thereof.

On the other hand, the international unity of science stabilized by the scientific ethos is a truly impressive phenomenon. Scientists from different cultures and social systems can readily engage in scientific communication. As long as they remain within the framework of science there will be no fundamental obstacles to mutual understanding.

The scientist can, of course, step out of this forum by expressing a *political* opinion or by talking *about* science but he must clearly reveal when he wishes to *persuade* (politically) and when he can offer *proof* (scientifically).

We thus face the question of how scientific knowledge influences social decision-making processes. The answer is not difficult to find. The contribution of science to the mastery of problems relating to human existence is always expressible in the form of "if-then" statements: given the constellation of factors x, then the consequences y will result; or, in order to achieve the consequences y then the constellation x must be brought about; or, if the consequences y are to be avoided then the constellation x must be avoided. Whether it is desirable or justifiable to achieve or avoid y is not implied by these propositions. Such a value judgment cannot be reached scientifically. Any *application* of scientific knowledge is therefore necessarily ambivalent. This is obvious from any piece of technology, whether a kitchen knife or penicillin, whether a herbicide or an atomic reactor. The moral responsibility of the scientist in his capacity as a scientist concerns only the reliability of the "if-then" propositions. However, this responsibility can hardly be overestimated because errors can cause immeasurable damage. *Reliable knowledge is a prerequisite for a right course of action.* Whether and in what situations a person applies "if-then" propositions to the solution of his problems nevertheless depends upon decisions lying outside the realm of science. Such decisions involve more than the addition of scientific "if-then" propositions. They also include the propensities, conventions, norms, motivations, and priorities which mold the actions of a state or society.

At this point we must consider that much-discussed question whether a scientist can contribute towards a more humane world by *withholding* knowledge. There have always been demands for a scientist's oath comparable with the Hippocratic Oath of medicine. Proposals for such an oath to be taken by the scientist are all based on the idea of committing oneself to work only on projects whose declared aim is compatible with particular value concepts—more humane value concepts. *Descartes* already had such an oath in view when he wrote, at the close of his "Discours": "I could not work on projects that are useful to some only by being harmful to others."

A contemporary proposal is due to *Dullart:* "Being admitted to the practice of the natural sciences I pledge to put my knowledge completely at the service of mankind. I shall prosecute my profession conscientiously and with dignity. I shall never collaborate in research aimed at the unjustified extermination of living organisms or the disturbance of the biological equilibrium which is harmful to mankind, neither shall I support such research in any way. Guide of my scientific work will be the promotion of the common welfare of mankind and in this context I shall not kill organisms nor shall I allow the killing of organisms for inferior, short-sighted, opportunistic reasons. I accept responsibility for unforeseen, harmful results directly originating from my work; I shall undo these results as far as lies in my power. This I vow voluntarily and on my word of honor."

The obstacles standing in the way of the introduction and implementation of such a commitment are obvious. How can a consensus be reached, and who will decide whether a given scientific project can be regarded as of service to mankind? Who would consider himself competent to make such a judgment? Take the Hippocratic Oath! The commitment to preserve human life under all circumstances and by all means has contributed essentially to the present situation in which the population explosion in many areas of the world represents a lethal threat to mankind, and the richness of genetic evolution, the variety and beauty of creation, have fallen victim to the exponential growth of man.

Any demand that the scientist should predict the possible consequences of his work and assume moral responsibility

for them *in advance* is unrealistic. Of course, *personal refusal* is a course open to everyone in a free society. Apart from very prominent heroic exceptions, however, it is ineffective because hardly anybody is indispensible in science.

As a variant of the Hippocratic Oath it is also argued that the expert scientist bears a *particular responsibility* for the common good. For example, one of the articles of the German Physical Society reads: "The Society commits itself and its members to take up the cause of freedom, veracity, and dignity in science, and to be conscious of the fact that those engaged in science bear a particularly high degree of responsibility for the shaping of the whole of human life". I consider the second part of this article to be an ill-considered empty phrase. *Particular* responsibility without *particular* legislative or executive power is, in a democracy, an unrealistic and morally dangerous postulate. A particular responsibility of the scientist would be feasible only if the scientist were to be assigned a *privileged* place in the legislative and executive. This is something I would oppose. Any swing towards technocracy and expertocracy affects the foundations of democracy and also overtaxes the scientist. Experience clearly refutes the idea that scientists are exceptionally qualified to formulate goals and to justify them ethically in areas lying *outside* their discipline. It is a flattering but false conclusion that scientific competence implies a high degree of normative reason. Most scientists have to learn sociopolitical thinking and action the hard way. It is certainly depressing to have to see how opportunism and shortsightedness gain ground among politicians. It is unnerving to see how the important decisions of our age overtax most people, and how the fear of progress and fear of risk also affects those who are not prepared to renounce progress. However, the alternative of wresting real power from the people, of a despotism bearing the trappings of moral respectability and appearing in the guise of a technocracy or expertocracy, is not acceptable. Science cannot provide an individual or a collective with a moral code, goals, or criteria which have the character and the validity of scientific propositions. Science has nothing to say about "the meaning of the world", about the "meaning of existence", or about the "aims of society". This is where the boundaries of science lie. We ought to respect them.

How can science overcome the crisis of confidence in which it is presently involved? I believe that there is only one answer. We must tell our fellow citizens in clear terms just what we can do and what we cannot. But first of all the scientist himself must clearly appreciate where scientific competence ends and presumptiousness starts. May I present an example.

Early in 1977, 650 scientists—physicists, chemists, biologists, physicians, engineers—from universities and research institutes all over West Germany declared the utilization of nuclear power to be both necessary and justifiable in an open letter addressed to the members of the German parliament. This source of energy represents the only short-to-medium-term way of adequately and inexpensively satisfying energy requirements even if all possible methods of saving energy are fully implemented and full use is made of domestic coal supplies. The 650 scientists were of the opinion "that the dangers of nuclear power are sufficiently under control and that this will also apply in the case of further expansion of nuclear power generation in view of the intense research work being performed on questions of safety". "The remaining residual risks" continues the letter "are taken seriously by us. However, they appear justifiable when set against the overall risk to civilization, and smaller than some other risks accepted as the price to pay for slighter advantages." Shortly afterwards, numerous other scientists—as they were called—signed a declaration demanding a drastic reduction and slow-down of existing nuclear power plant planning. The reasons given were, *inter alia*, that the safety problems accompanying the large-scale exploitation of nuclear power can by no means be regarded as solved. The consequences of plutonium production were cited. Police-state methods would be required to prevent the theft and misuse of plutonium. Moreover, the export of nuclear power plants by the Federal Republic of Germany creates further possibilities of misuse. Most of the signatories of this declaration were not scientists or technologists competent in the issues at stake, but sociologists, theologians, and publicists. And yet reports about the declaration appeared in the press and on television under the headline "one thousand scientists issue warning". Parliamentarians at Bonn faced two opposing declarations, both claiming to speak in the name of science. Since the mass media in the Federal Republic gave wide coverage with accompanying commentary only to the "Declaration of the sixteen-hundred", the public, already uneasy about nuclear energy, gained the impression that *science* almost entirely rejects the expansion of nuclear power generation capacity.

We cannot go on in this way. For the sake of science we must counter the hubris that scientists are the moral watchdogs of society and arbitrators in matters of political conscience. In making this claim of "critical science" the university has overstepped its limits. Science cannot tell people what is "good" and what is "beautiful", or where human life and the human race are going. Questions about "sense" and "purpose" cannot be definitively answered in the framework of science. Knowledge is a prerequisite, but is not a sufficient reason, for right action or for the right conduct of our lives.

Has science failed?—No, with regard to its effectiveness and its ethos. Yes, inasmuch as it has failed and continues to fail to give account of its limitations.

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Communications are brief preliminary reports of research work in all areas of chemistry which, on account of its fundamental significance, novelty, or general applicability, should be of interest to a broad spectrum of chemists. Authors of communications are requested to state reasons of this kind justifying publication on submission of their manuscript. The same reasons should be clearly apparent from the manuscript. In cases where the editorial staff decide, after due consultation with independent referees, that these conditions are not met, manuscripts will be returned to the authors with the request to submit them for publication in a specialist journal catering for scientists working in the field concerned.

Mild Oxidative Removal of the *p*-Methoxybenzyl Ether Protecting Group by Homogeneous Electron Transfer[1]

By *Werner Schmidt* and *Eberhard Steckhan*[*]

The benzyl ether function is one of the most common protecting groups for alcohols. It is usually removed by catalytic hydrogenation or less often by sodium in liquid ammonia[2]. If, however, the substrate contains additional reducible functions, this procedure is unsatisfactory.

We now report a simple and mild method for the removal of the *p*-methoxybenzyl ether protecting group by homogeneous electron transfer under *oxidative* conditions. The stable cation radical of tris(*p*-bromophenyl)amine is employed as electron transfer agent (mediator). Bond cleavage takes place in moist acetonitrile according to the following reaction scheme:

$$\underset{(1)}{(Br\text{-}C_6H_4)_3N^{\bullet\oplus}} + \underset{(3)}{RO\text{-}CH_2\text{-}R'} \rightleftharpoons \underset{(2)}{(Br\text{-}C_6H_4)_3N} + \underset{(4)}{[RO\text{-}CH_2\text{-}R']^{\bullet\oplus}} \quad (a)$$

$$\underset{(4)}{} + H_2O \rightleftharpoons RO\text{-}\dot{C}H\text{-}R' + H_3O^{\oplus} \quad (b)$$
$$(5)$$

$$\underset{(1)}{} + \underset{(5)}{} \rightleftharpoons RO\text{-}\overset{\oplus}{C}H\text{-}R' + \underset{(2)}{} \quad (c)$$
$$(6)$$

$$\underset{(6)}{} + H_2O \rightarrow ROH + R'CHO + H^{\oplus} \quad (d)$$

$R' = -C_6H_4-OCH_3$

The reversible potential of the redox couple *(1)*/*(2)* ($E^0 = +1.05$ V *vs.* SCE) is about 550 mV more negative than the irreversible oxidation potentials of the ethers *(3)*[3]. The driving force of the reaction is the deprotonation step (b). By addition of 2,6-dimethylpyridine the bond cleavage can be substantially accelerated[4].

The cation radical *(1)* can either be used in stoichiometric amounts as its readily obtainable[5] stable hexachloroantimonate (method 1), or it can be electrochemically generated and regenerated from the amine during the course of the reaction (method 2). In the latter case only catalytic amounts of the electron transfer agent are necessary.

Both methods usually give good to excellent yields and the alcohol is obtained in high purity. In contrast to the reductive deprotection procedures, double bonds are not attacked. Numerous oxidation-labile functions should tolerate the new procedure because the redox potential of the mediator is very low. Direct anodic deprotection, however, needs an anode potential of at least +1.6 V *vs.* SCE and fouling of the electrode is often encountered[6].

Table 1. Oxidative cleavage of the *p*-methoxybenzyl ether protecting group by homogeneous electron transfer.

$RO\text{—}CH_2\text{—}C_6H_4OCH_3$ *(3)* R	Yield of R—OH [%] [a] Method 1	Method 2
1-Octyl	86	95
1-Methylheptyl	81	87
E-4-Hepten-1-yl	75	83

[a] Material yield.

General procedure

Method 1: To a solution of 2 mmol of the respective *p*-methoxybenzyl ether *(3)* (2 mmol) and 2,6-dimethylpyridine (0.212 g, 2 mmol) in CH_3CN[7]/CH_2Cl_2 (5:1) a solution of tris(*p*-bromophenyl)ammoniumyl hexachloroantimonate (4.08 g, 5 mmol) in CH_3CN/CH_2Cl_2 (5:1) is added dropwise until the blue colour of the cation radical *(1)* persists. For product workup, water is added to the reaction solution which is subsequently reduced, saturated with KCl, and extracted with ether. After extraction with $NaHSO_3$ solution the ether phase is dried over $MgSO_4$. The alcohols are identified by gas chromatography and mass spectrometry on comparison with authentic samples and isolated by bulb-to-bulb distillation.

Method 2: In a divided beaker-type glass cell (20 °C, Pt anode, Pt cathode) a solution of tris(*p*-bromophenyl)amine (0.964 g, 2 mmol) in CH_3CN/CH_2Cl_2 (5:1; 0.2 M $LiClO_4$) is used as anolyte. The catholyte consists of CH_3CN/1.0 M $LiClO_4$. After application of an anode potential of +1.2 V (*vs.* Ag/AgCl) the blue color of *(1)* appears. When the respective *p*-methoxybenzyl ether *(3)* (5 mmol) and 2,6-dimethylpyridine (0.535 g, 5 mmol) are added the solution is decolorized. After reappearance of the blue color of the electron transfer agent (consumption of about 0.013 F) the electrolysis is stopped. The workup procedure is the same as in method 1.

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CAS Registry numbers:
(1), 37881-41-7; *(1)* hexachloroantimonate, 24964-91-8; *(2)*, 4316-58-9; *(3)* (R = octyl), 54384-75-7; *(3)* (R = 1-methylheptyl), 54384-76-8; *(3)* (R = *E*-4-hepten-1-yl), 67523-82-4

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[1] Indirect Electrochemical Processes, Part 4. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 3: *W. Schmidt, E. Steckhan*, J. Electroanal. Chem. *89*, 215 (1978).
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[7] Acetonitrile (Merck), water content 0.5%.

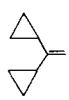
Influence of Cyclopropyl Substituents on the Relative Rate of Dichlorocarbene Addition to Olefins[**]

By *Eckehard V. Dehmlow* and *Axel Eulenberger*[*]

Enormous rate enhancements caused by cyclopropyl rings adjacent to developing positive charges are well known. However, the influence of cyclopropane on additions to double bonds is less clear: In hydratation and bromination, cyclopropane accelerates relative to *n*-butyl by about 10^4[1], and in cycloadditions with tetracyanoethylene and arylsulfonyl isocyanates accelerations of 10^3 are found[2]. Only small differences are observed, however, when arylsulfenyl chlorides are added[1]. In the ene-reaction with singlet oxygen, the electronic effect of cyclopropane is comparable with that of methyl[3].

We subjected a number of cyclopropylalkenes to reaction with dichlorocarbene generated by phase-transfer catalysis[4] and characterized the products. The same olefins were subsequently employed in competition experiments with less than equivalent amounts of dichlorocarbene. Analysis was performed by gas chromatography after calibration for each of the products determined in the preliminary experiments. Table 1 shows the reactivities (±5%) relative to 3,3-dimethyl-1-butene *(14)*. Steric and electronic effects seem to counteract each other. A cyclopropyl ring exerts a powerful accelerating effect compared to its open-chain analog [*(10)/(12)*, *(11)/(14)*, *(5)/(13)*] but—depending on the steric situation—this effect is somewhat more [*(2)/(4)*] or somewhat less pronounced [*(3)/(1)*, *(5)/(4)*] than that of methyl. Furthermore, the effect of a double bond is roughly comparable to that of a three-membered ring. 1-Methylcyclopropyl compounds [*(6)/(11)*] are less reactive than the unsubstituted compounds [*(2)/(10)*] for steric reasons.

Table 1. Relative reactivities of various alkenes towards dichlorocarbene.

	Alkene	Rel. reactivity		Alkene	Rel. reactivity
(1)		2035	*(8)*		200
(2)		1415	*(9)*	 [b]	140
		970	*(10)*		100
(4)		950	*(11)*		76
(5)		910	*(12)*		12
(6)		830	*(13)*		9
(7)	 [a]	744	*(14)*		1

[a] Addition to methyl-substituted double bond.
[b] Monoaddition.

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CAS Registry numbers:
(1), 18738-69-7; *(2)*, 4663-22-3; *(3)*, 23603-63-6; *(4)*, 115-11-7; *(5)*, 822-93-5; *(6)*, 78-79-5; *(7)*, 3422-07-9; *(8)*, 110-83-8; *(9)*, 106-99-0; *(10)*, 693-86-7; *(11)*, 16906-27-7; *(12)*, 563-45-1; *(13)*, 16746-02-4; *(14)*, 558-37-2; dichlorcarbene, 1605-72-7

[1] *D. G. Garratt, A. Modro, K. Oyama, G. H. Schmidt, T. T. Tidwell, K. Yates*, J. Am. Chem. Soc. *96*, 5295 (1974).
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Dimethylsilanediyliron Complexes[1]

By *Hideki Sakurai, Yoshiyasu Kamiyama*, and *Yasuhiro Nakadaira*[*]

Schmid et al.[2] recently reported the preparation of *base-stabilized* silanediyliron complexes. We now wish to communicate our observations on the first *stable* mononuclear dimethylsilanediyliron complexes.

When a yellow-orange suspension of $Fe_2(CO)_9$ (1.00 g, 2.75 mmol) and pentamethyldisilane *(1)* (498 mg, 3.77 mmol) in benzene (10 ml) was stirred at room temperature for 15 h under argon, a yellow-brown homogeneous solution was obtained, from which a yellow-orange complex tricarbonylhydrido(dimethylsilanediyl)trimethylsilyliron *(3)* (523 mg, 1.92 mmol) was isolated in 70% yield as an oil, b.p. 30 °C/0.005 torr.

$$Fe_2(CO)_9 + H\text{–}SiMe_2\text{–}SiMe_2R \longrightarrow Me_2Si{=}Fe(H)(CO)_3 + \ldots \quad (SiMe_2R)$$

(1), R = Me; *(2)*, R = H

(3), R = Me; *(4)*, R = H

The complex *(3)* is extremely air-sensitive and decomposes instantaneously on exposure to air, but correct elemental analyses are obtained on careful handling. The ^{1}H-NMR (CS_2) spectrum of *(3)* shows, in addition to the FeH signal at

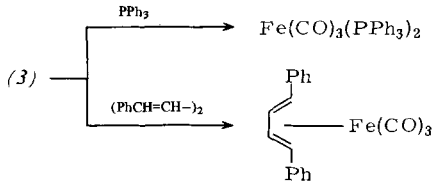
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$\delta = -9.41$, two Si—CH_3 signals at $\delta = 0.36$ and 0.71 with a relative intensity of 3 : 2. The signal at $\delta = 0.71$ can be assigned to the terminally bonded Me_2Si group, since all the $SiCH_3$ signals of bridging Me_2Si groups in dinuclear complexes appear at lower field[3].

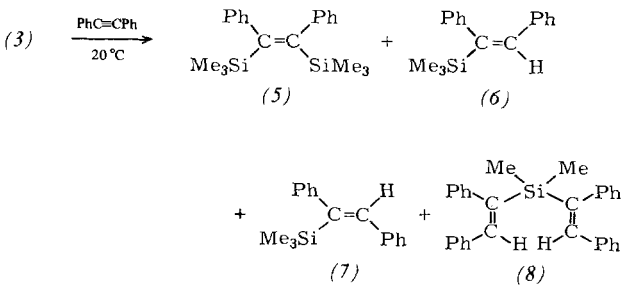
The mass spectrum of *(3)* (25 eV) shows the molecular ion at *m/e* 272 (5.0 %) and ions corresponding to the successive loss of CO leading to Me_2SiFe^+ (*m/e* = 114, 23.8 %) and Me_3Si^+ (*m/e* = 73, 100 %). In the νCO region of *(3)* there appear four bands at 2080 (s), 2030 (s, sh), 2000 (vs), and 1930 (s, sh) cm^{-1}.

Similar reaction of $Fe_2(CO)_9$ and 1,1,2,2-tetramethyldisilane *(2)* gave the corresponding yellow-orange complex *(4)*; b.p. 23 °C/5 × 10^{-3} torr. IR (neat): 2080 (s), 2030 (s, sh), 2000 (vs), 1930 (s, sh) cm^{-1}; MS (25 eV): *m/e* 258 (M^+, 11.4 %), 114 (100 %); ^{1}H-NMR (CS_2): $\delta = -9.4$ (1 H, s, Fe—*H*), 0.30 (6 H, d, *J* = 4.0 Hz, SiH—CH_3), 0.7 (6 H, s, Si—CH_3), 4.0 (1 H, sept., *J* = 4.0 Hz, Si—*H*).

The complex *(3)* reacts with triphenylphosphane and 1,4-diphenylbuta-1,3-diene to give the respective substitution compounds:



The reaction of *(3)* with diphenylacetylene results in the formation of several interesting compounds as shown in the following scheme:



+ $Fe(CO)_3(PhC{\equiv}CPh)_2$ + $Fe_2(CO)_7(PhC{\equiv}CPh)_2$
(9) *(10)*

(5) (6 %), *(6)* (20 %), *(7)* (2 %), *(8)* (5 %), *(9)* (7 %), and *(10)* (8 %) were isolated by TLC on silica gel.

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(1), 812-15-7; *(2)*, 814-98-2; *(3)*, 67505-78-6; *(4)*, 67505-77-5; *(5)*, 53511-09-4; *(6)*, 57266-93-0; *(7)*, 57266-94-1; *(8)*, 67489-32-1; *(9)*, 67505-79-7; *(10)*, 67523-52-8; $Fe(CO)_3(PPh_3)_2$, 14741-34-5; (Ph—CH=CH—CH=CH—Ph)$Fe(CO)_3$, 33593-85-0; $Fe_2(CO)_9$, 15321-51-4; PhC≡CPh, 501-65-5

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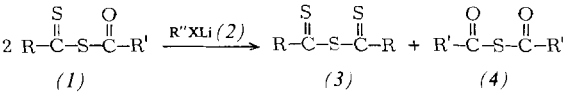
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Bis(thioacyl) Sulfides from Acyl Thioacyl Sulfides

By *Shinzi Kato, Katsumi Sugino, Masateru Mizuta*, and *Tomonori Katada*[*]

Bis(thioacyl) sulfides *(3)* are accessible by reaction of dithiocarboxylic acids and dicyclohexylcarbodiimide[1]. In the course of a study on the synthetic utility of acyl thioacyl sulfides *(1)*, it was found that compounds *(3)* are obtained in fair yield by treatment of *(1)* with lithium alkoxides or alkyl sulfides *(2)*. Preliminary experiments revealed that the yields of *(3)* are highly dependent upon the group R′ and upon the species *(2)*. The highest yield was obtained on reaction of *(1a)* with lithium ethyl sulfide. The reaction proceeds even on use of 1/3 mol of lithium salt per mol of *(1a)* to give over 60 % of *(3a)* (Table 1). This reaction also gives bis(acyl) sulfide *(4)*, which was detected IR spectroscopically.



R = Alkyl, Aryl
R′ = Alkyl
X = O, S

Table 1. Reaction of acyl(thioacyl) sulfides with lithium alkoxides or alkyl sulfides.

	R	R′	R″X	*(1)* : *(2)*		M.p. [°C]	Yield [%]
(1a)	4-CH_3—C_6H_4	CH_3	C_2H_5S	1 : 1	*(3a)*	74	76
(1a)	4-CH_3—C_6H_4	CH_3	C_2H_5S	1 : 0.3	*(3a)*		>60
(1b)	4-CH_3—C_6H_4	C_2H_5	C_2H_5S	1 : 1	*(3a)*		22
(1a)	4-CH_3—C_6H_4	CH_3	C_2H_5O	1 : 1	*(3a)*		48
(1a)	4-CH_3—C_6H_4	CH_3	C_6H_5S	1 : 1	*(3a)*		33

This is the first example of a base-catalyzed disproportionation reaction of acyl thioacyl sulfides.

Experimental

To a solution of *(1a)*[2] (0.42 g, 2 mmol) in *n*-hexane (30 ml) was added lithium ethyl sulfide (0.14 g, 2 mmol) and the mixture was stirred for 30 min at 0 °C under argon. The sky-blue solution becomes dark blue within 5 min, and formation of small amounts of green crystals is observed. Insoluble EtSLi is filtered off, and the filtrate is concentrated to *ca.* 15 ml *in vacuo*. Cooling to −50 °C gave a green precipitate of *(3a)* which was isolated by filtration [yield 0.25 g (76 %); m.p. 74 °C (74–75 °C[1a])] (76 %) and identified by comparison with an authentic sample[1a] (IR, UV, ^{1}H-NMR).

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Facile Synthesis of 2-Aryl- and 2-Heteroarylpyrroles from *N*-Allylcarboxamides

By *Norbert Engel* and *Wolfgang Steglich*[*]

2-Aryl- and 2-heteroarylpyrroles are of interest as precursors for the synthesis of chemotherapeutics[1]. The syntheses hitherto described in the literature, however, are laborious and afford only moderate yields[2]. We have found that the pyrroles *(5)*, R^1 = aryl, heteroaryl, *tert*-alkyl, can be prepared in high yields from the imidoyl chlorides *(2)*[3]—readily available from *N*-allylcarboxamides *(1)*—by cyclization with potassium *tert*-butoxide in an inert solvent (Table 1)[4].

Special purification of *(2)* is not essential. Hence, this method provides convenient access to 2-(2-furyl)pyrrole *(5b)* and 2-(2-thienyl)pyrrole *(5c)*[5].

The cyclization to the pyrrole ring can be interpreted in terms of a 1,5 dipolar ring closure of the nitrile ylide *(3)*[6] formed by elimination of HCl from *(2)*, the primary product *(4)* subsequently isomerizing to *(5)*[7]. In the case of *N*-allylimidochlorides of the aliphatic acids bases promote elimination of HCl to give the ketenimines, which subsequently rearrange into γ,δ-unsaturated nitriles[8]. This novel method for the synthesis of pyrroles is therefore limited to allylamides of carboxylic acids which do not contain an H atom in the α-position.

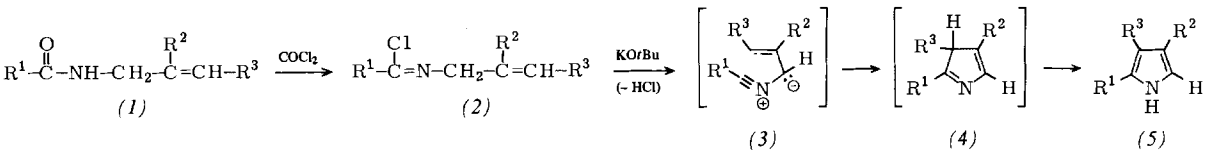
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CAS Registry numbers:

(1a), 10283-95-1; *(1b)*, 63122-36-1; *(1c)*, 63122-31-2; *(1d)*, 63122-38-3; *(1e)*, 109-25-1; *(1f)*, 63163-3; *(2a)*, 39887-72-4; *(2b)*, 63122-39-4; *(2c)*, 63122-40-7; *(2d)*, 63122-41-8; *(2e)*, 63148-39-0; *(2f)*, 63122-42-9; *(5a)*, 3042-22-6; *(5b)*, 63122-43-0; *(5c)*, 52101-46-7; *(5d)*, 5398-58-3; *(5e)*, 20055-04-3; *(5f)*, 26093-30-1.

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Table 1. Pyrroles *(5)* from *N*-allylcarboxamides *(1)* [a].



(1) *(2)* *(3)* *(4)* *(5)*

(1)	R^1	R^2	R^3	Yield [b] [%]	M.p. [°C], B.p. [°C/torr]	*(5)*	Yield [c] [%]	M.p. [°C], B.p. [°C/torr]
(1a)	C_6H_5	H	H	91	113—115/0.05	*(5a)*	86 A	130 (cyclohexane)
(1b)	2-Furyl	H	H	93	87 (bath temp.)/0.05	*(5b)*	86 B	44 (subl. in vac.)
(1c)	2-Thienyl	H	H	86	65 (ether)	*(5c)*	86 A	78 (subl. in vac.)
(1d)	$(CH_3)_3C$	H	H	92	108/17	*(5d)*	87 B	65—66/17
(1e)	C_6H_5	CH_3	H	81	86 (toluene/petroleum ether)	*(5e)*	61 B	154 (cyclohexane)
(1f)	C_6H_5	H	C_6H_5	87	94 (toluene/petroleum ether)	*(5f)*	60 A	129 (cyclohexane)

[a] *(1a)*, *(1e)*, *(1f)*, *(5a)*, *(5d)*, *(5e)*, *(5f)* are well documented in the literature. The remaining compounds gave correct elemental analyses and spectroscopic data consistent with the given structures.
[b] Prepared from amine and acyl chloride in aqueous hydrogen carbonate at 0—5°C.
[c] A: referred to *(1)*; B referred to distilled imidoyl chloride: *(2a)*, yield 91%, b.p. 71°C/0.05 torr; *(2b)*, 84%, b.p. 68°C (bath temperature)/0.05 torr; *(2d)*, 74%, b.p. 53°C/17 torr.

General procedure

Synthesis of *(2)*: A mixture of *(1)* (10 mmol), a 20% solution of phosgene in toluene (20 ml), and 2 drops of dimethylformamide is stirred for *ca.* 15 h at room temperature. The solution is then heated to 40—50°C and the toluene removed *in vacuo* simultaneously. The residue is distilled *in vacuo* and stored, or used directly for further syntheses.

Synthesis of (5): A solution of *(2)* (10 mmol) in tetrahydrofuran (10 ml) is added dropwise at 5—10°C under N_2 to a solution of potassium *tert*-butoxide (30 mmol) in dimethylformamide (15 ml) [in the case of *(2f)* dimethyl sulfoxide and 90°C]. 10 minutes after completion of addition the violet to black reaction solution is poured into a 20-fold amount of ice-water and then extracted with ether. After removal of solvent the extract is purified by steam distillation and/or recrystallization.

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cyclo-Triarsenic as μ,η-Ligand in Transition-Metal Complexes

By *Massimo Di Vaira, Stefano Midollini, Luigi Sacconi*, and *Fabrizio Zanobini*[*]

On reaction of white phosphorus P_4 with hydrated cobalt(II) and nickel(II) salts in the presence of 1,1,1-tris(diphenylphosphinomethyl)ethane, $CH_3C(CH_2PPh_2)_3$ (triphos), we recently obtained the first metal complexes containing *cyclo*-triphosphorus (δ-P_3) as a ligand[1]. This finding prompted us to

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try to synthesize the corresponding complexes of *cyclo*-triarsenic (δ-As_3) by an analogous procedure using yellow arsenic (As_4). Elementary As_4 is extremely unstable and readily converts into the gray form, particularly on exposure to light. To overcome this difficulty we have employed a THF solution of yellow arsenic prepared by an improved method based on that described by *Erdmann et al.*[2].

This As_4 solution reacts smoothly with Co^{II} or Ni^{II} aquo-ions and the trisphosphane in THF/ethanol/acetone solution to give the As_3 complexes of general composition [(triphos)M-μ-(η-As_3)M(triphos)]X_2 (M = Co, Ni; X = BF_4, BPh_4). The new compounds have a triple-decker sandwich structure containing the bridging *cyclo*-triarsenic entity as an internal layer. The salts behave as 1 : 2 electrolytes and are exceptionally air stable, both in the solid state and in solution (acetone, nitroethane, *etc.*). The magnetic moments of both the cobalt and the nickel dinuclear units correspond to the existence of one unpaired electron for each unit.

An X-ray structural investigation has been undertaken on the compound [(triphos)Co-μ-(η-As_3)Co-(triphos)]$(BPh_4)_2$, which crystallizes with two molecules of acetone[3]. The complex cation possesses a triple-decker sandwhich structure in which the *cyclo*-triarsenic unit forms the internal slice

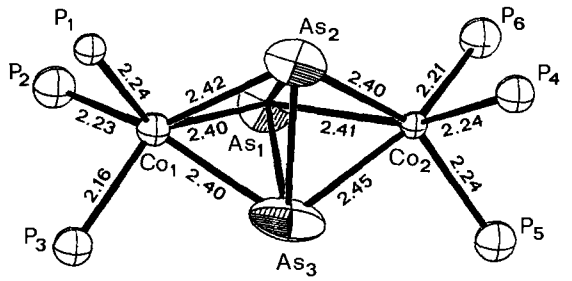


Fig. 1. Structure of the $[(triphos)Co(As_3)Co(triphos)]^{2+}$ dication with bond lengths [Å]. Bond angles: P—Co—P = 90—93°, As—Co—As = 60—61°.

(Figure 1). Each cobalt atom is six-coordinated by the three phosphorus atoms of one triphos ligand and by the three arsenic atoms of the bridging *cyclo*-triarsenic group.

The magnetic moments of these cobalt and nickel complexes, both correspond to a doublet ground state; in a qualitative MO model[4], the highest-occupied orbital (e, C_3-symmetry) contains one and 3 electrons, respectively. The two compounds are classified as 31 and 33-electron triple-decker complexes, 12 electrons being supplied by the donor atoms of the two triphos ligands, 3 by the *cyclo*-triarsenic ligand, the other electrons in the valence shell being provided by the two metal atoms. A mononuclear cobalt complex containing the As_3 ring as ligand, $As_3Co(CO)_3$, had already been synthesized by *Dahl et al.*[5] by reaction of $Co_2(CO)_8$ with $(AsCH_3)_5$.

Procedure

7 g of gray arsenic is heated for *ca.* 90 min at 560—580 °C (cf. [2]). The vapor of yellow arsenic is absorbed at *ca.* 0 °C in 250 ml of THF, the solution filtered and then concentrated to 150 ml in the dark, in a nitrogen stream, at room temperature. To this solution is added 0.680 g (2 mmol) of $Co(BF_4)_2 \cdot 6H_2O$ in 20 ml of ethanol and 1.25 g (2 mmol) of "triphos" in 30 ml of acetone. The resulting mixture is heated in the dark on a water-bath under a stream of nitrogen for 20 min, then concentrated in the light to *ca.* 30 ml by passage of nitrogen. The dark-green crystals which separate are filtered off and then dissolved in 50 ml acetone. To this solution is added 0.680 g (2 mmol) of $NaBPh_4$ in 20 ml ethanol. On concentration of the solution, black-green crystals precipitate. These are filtered off, washed with THF and ethanol, and dried in *vacuo*. Yield 75 %.

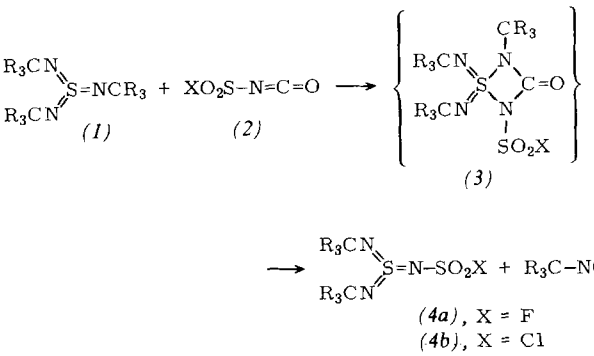
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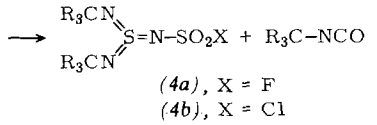
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Synthesis of 1λ⁶,2,4-Thiadiazetidin-3-ones from Tris(imido)sulfur(VI) Derivatives and Sulfonyl Isocyanates[**]

By *Frank-Michael Tesky, Rüdiger Mews, Bernt Krebs*, and *M. Ramakrishna Udupa*[*]

Characteristic reactions of sulfur compounds belonging to the "Y-triene" type $(RN{=})_3S$[1] involve an increase in the coordination number of the central S^{VI} atom[2]. We expected the reaction of the *tert*-butyl derivative *(1)*, R = CH_3, with sulfonyl isocyanates *(2)* to yield the cycloaddition products *(3)*.





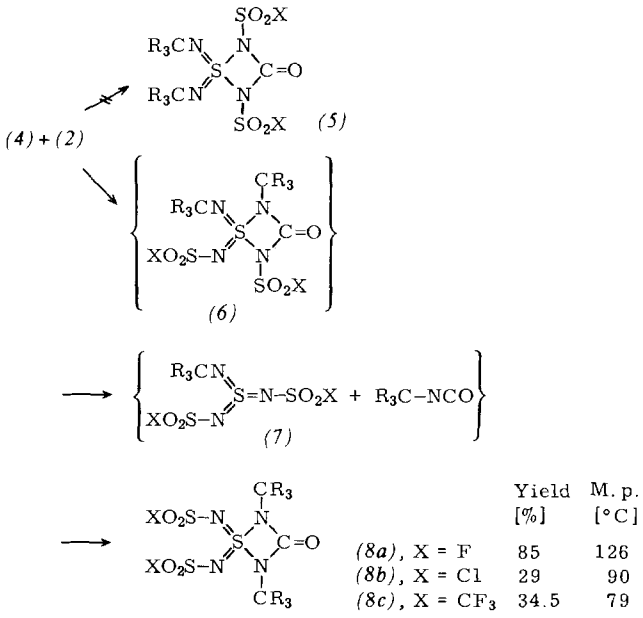
However, thiadiazetidinones *(3)* bearing a strongly electronegative substituent on the ring nitrogen are unstable; like their S^{IV} analogs[3] they decompose with elimination of alkyl isocyanate. On reaction of *(1)* with an only slight excess of *(2)*, X = F, Cl, the corresponding monosulfonylimidosulfur(VI) compounds *(4)* can be isolated in good yields. The colorless solids *(4a)*, m.p. 55 °C, and *(4b)*, m.p. 91 °C, are stable for a long time at 0 °C. Thus the possible syntheses of "Y-trienes" $(RN{=})_3S$ are not restricted to derivatives with bulky groups R.

An excess of *(2)* reacts further with *(4)* to give the symmetrical thiadiazetidinones *(8)*.

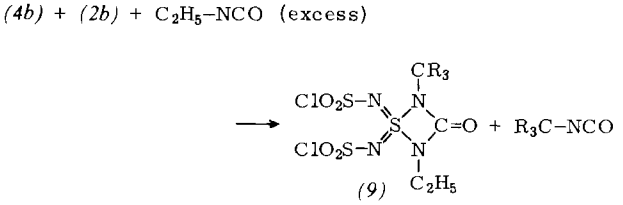
The formation of *(6)* rather than *(5)* as the next addition product follows from the structure of the final product *(8)*.

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Formation of *(9)* in the presence of a large excess of ethyl isocyanate is regarded as evidence for the intermediacy of *(7)*:



Compounds *(8)* were characterized by elemental analysis, as well as mass, IR, and NMR spectra. The ^{1}H- and ^{19}F-NMR spectra contain only singlets [*(8a)*: $\delta_{SF} = +60.7$, $\delta_{CH} = +1.646$; *(8b)*: $\delta_{CH} = +1.646$; *(8c)*: $\delta_{CF} = -78.1$, $\delta_{CH} = +1.625$]; as in other four-membered ring ketones[4], the CO stretching vibrations appear at high wavenumbers [ν_{CO}: *(8a)* 1840, *(8b)* 1842, *(8c)* 1840 cm^{-1}]. The spectroscopic data hardly permit any distinction between *(8)* and *(5)*; it took an X-ray structure analysis performed on *(8a)* to rule out the alternative *(5)*.

(8a) forms orthorhombic crystals [Pnma, $a = 16.075(4)$, $b = 12.990(3)$, $c = 8.071(2)$ Å; at -120 °C: $P2_12_12_1$, $a = 15.936(4)$, $b = 12.794(3)$, $c = 7.934(2)$ Å, $Z = 4$]. The structure was solved from low-temperature diffractometer data by direct methods and refined to $R = 2.8$ %. Figure 1 depicts the molecule with averaged bond parameters. The mutually perpendicular fragments SN=S=NS and C–N<C,S>N–C are almost planar (angles in ring: NSN 79.5(1), SNC 92.0(2), NCN 96.5(2)°).

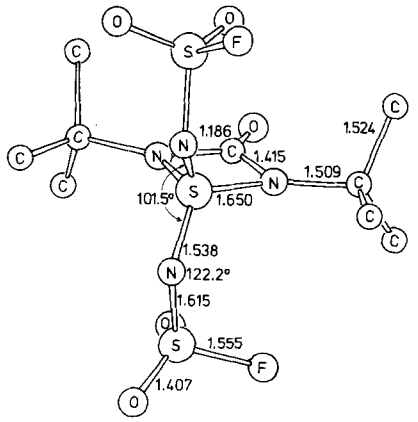


Fig. 1. Molecular structure of crystalline thiadiazetidinone *(8a)* with bond lengths and angles (standard deviation 0.002 to 0.004 Å and 0.2°, respectively).

Procedure

a) Bis(tert-butylimido)halosulfonylimidosulfur(VI) (4): A solution of halosulfonyl isocyanate *(2)* (8.4 mmol) in pentane (60 ml) is added dropwise at +10 °C to *(1)* (2.0 g, 8.16 mmol) in pentane (120 ml). After stirring for 16 h, the resulting colorless solution is decanted from the polymer adhering to the vessel wall and cooled to −100 °C. The precipitated product is filtered off at this temperature under nitrogen. Yield 58 % *(4a)* [NMR: $\delta_{SF} = +54.0$ (s), $\delta_{(CH_3)_3C} = +1.46$ (s); MS: $m/e =$ 271 (2.3 %) M^+] and 63 % *(4b)* [NMR: $\delta_{(CH_3)_3C} = +1.49$ (s); MS: $m/e = 287$ (1.5 %) M^+].

b) 1λ^6,2,4-Thiadiazetidin-3-ones (8): Analogous reaction of *(1)*, but with 24.8 mmol of sulfonyl isocyanate. *(8a)* is purified by sublimation (oil pump vacuum, 50–55 °C); *(8b)* and *(8c)* by crystallization from pentane [MS: M^+ at $m/e = 396$ (2.3 %), 428 (2.0 %), and 496 (1.8 %), respectively].

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(1), 64011-17-2; *(2)* (X=F), 1495-51-8; *(2)* (X=Cl), 1189-71-5; *(3)* (X=F), 67506-32-5; *(3)* (X=Cl), 67506-33-6; *(4a)*, 67506-34-7; *(4b)*, 67506-35-8; *(8a)*, 67506-36-9; *(8b)*, 67506-37-0; *(8c)*, 67506-38-1

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Elimination of CH_3 from the Radical Cation of Methyl Isobutyrate: Fast C—C Cleavage after Rate-Determining H-Migration[**]

By *Chrysostomos Wesdemiotis* and *Helmut Schwarz*[*]

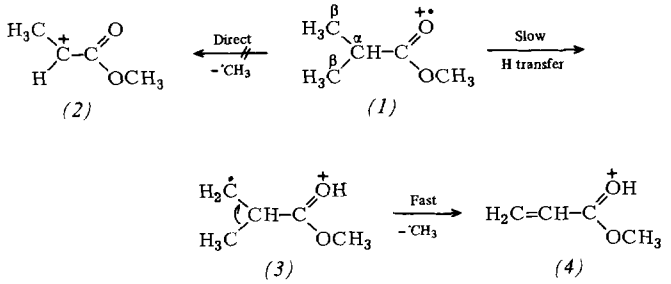
Electron impact induced dissociations, which are actually the result of special neighboring group effects (*e.g.* anchimeric participations[1a] or *ortho*-effects[1b]), have already been reported in the literature on several occasions[1c]. We report here on the first example of a system in which the rupture of a C—C bond cannot be described in terms of a simple homolysis, but rather in terms of an intramolecular, rate-determining H-migration[2].

On electron impact ionization (70 eV) of methyl isobutyrate *(1)* the mass spectrum shows an intense signal for the methyl elimination from $M^{+\bullet}$ (13 % total ion current (TI)). In the case of unimolecular dissociation of *metastable* molecular ions of *(1)* the intensity increases to 77 %. In accord with theoretical predictions[3] this would indicate that the CH_3 elimination must be particularly favorable energetically and *cannot* proceed *via* a simple α-cleavage with formation of an energy-rich α-ketocarbenium ion *(2)*. Experiments with ^{13}C- or ^{2}H-labeled methyl isobutyrates *(1a)*—*(1d)* confirm (i) that the

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carbon atom of the eliminated methyl radical stems *specifically* from a β-C atom and (ii) that the hydrogen of the neutral moiety derives almost exclusively from the β-methyl group. Slight contributions from the ester function can be attributed to incomplete H/D exchange in $M^{+\bullet}$. The fact that formation of $^{\bullet}CD_3$ predominates (66 % together with 9 % $^{\bullet}CD_2H$) over that of $^{\bullet}CH_3$ (25 %) in the unimolecular decomposition of *(1d)* cannot be explained in terms of a *secondary* inverse kinetic isotope effect, since this would be at least an order of magnitude smaller[4].



(2) *(1)* *(3)* *(4)*

Assumption that the elimination of a methyl group from *(1)* proceeds in *two steps* would provide a plausible explanation for all the experimental findings. In the *rate-determining* step a hydrogen atom is transferred from a β-methyl group to the ionized carbonyl group, thus generating the reactive intermediate *(3)*. This is followed by *fast* radical-induced homolysis *(3)* → *(4)*; the protonated methyl acrylate *(4)* is relatively stable in comparison with *(2)*. If, however, the H-transfer *(1)* → *(3)* is rate-determining for the overall reaction then in the case of *(1d)* the reactive intermediate *(3)* ought to be generated preferably by H-transfer over D-transfer—with the consequence that *mainly* $^{\bullet}CD_3$ will be eliminated (after H-transfer) and *to a lesser extent* $^{\bullet}CH_3$ (after D-transfer). Precisely this is observed (Table 1).

Table 1. Unimolecular methyl-elimination from methyl isobutyrate, with and without isotopic labeling [a].

		$^{12}CH_3$	$^{12}CD_3$	$^{12}CD_2H$	$^{12}CDH_2$	$^{13}C^{1}H_3$
$(CH_3)_2CHCOOCH_3$	*(1)*	100	—	—	—	—
$(^{13}CH_3)_2CHCOOCH_3$	*(1a)*	—	—	—	—	100
$(^{13}CH_3{}^{12}CH_3)CHCOOCH_3$	*(1b)*	52	—	—	—	48
$(CH_3)_2CHCOOCD_3$	*(1c)*	97	—	—	3	—
$(CD_3CH_3)CHCOOCH_3$	*(1d)*	25	66	9	—	—

[a] The data quoted in % (average value of 5 measurements) are based on total methyl-elimination (= 100 %); the measurements were carried out using the MIKES-technique [8] (mass spectrometer: Varian MAT 311 A).

A further experimental indication that the cleavage of methyl from *(1)* proceeds in two steps is afforded by a peak-shape analysis of the kinetic energy release (T_{kin}) in the unimolecular dissociation of metastable ions. Theoretically[3, 5], for a multistep reaction in which the actual decomposition is preceded by a rate-determining isomerization, T_{kin} ought to be greater than for analogous reactions which proceed in one step or in which the isomerization is not rate-determining. The measured T_{kin} value of 0.9 kcal·mol^{-1} is at least an order of magnitude too large for a simple C—C cleavage[3b, 6]; however, it lies in the range that would appear to be typical for dissociation processes in which either extremely stable product ions are generated[6] or the actual bond rupture is initiated by H-transfer[1b, 7].

Definite proof that the $[M-CH_3]^+$ ion of *(1)* (*m/e* = 87) has the structure *(4)* is provided by collision activation spectroscopy (CA spectroscopy[9]): the CA spectrum of the ion of *(1)* with *m/e* = 87 is identical with that of an independently generated ion of structure *(4)* (fingerprint criterion) and shows the structure-specific fragments for *(4)*, *e.g.* $H_2C{=}\overset{+}{C}H$.

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(1), 67505-84-4; *(1a)*, 67505-85-5; *(1b)*, 67505-86-6; *(1c)*, 67505-87-7; *(1d)*, 67505-88-8; *(4)*, 67457-05-0

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Reactions of Nucleosides with the Triphenylphosphane/Diethyl Azodicarboxylate System[**]

By *Rudolf Mengel* and *Michael Bartke*[*]

Oxidation-reduction condensations with the triphenylphosphane/diethyl azodicarboxylate (TPA) system have recently found wide application[1-4], *inter alia*, in the esterification of alcohols. It is assumed that alkoxyphosphonium ions are formed as intermediates which react as strong alkylating agents with nucleophiles[2].

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[**] Nucleoside Transformations, Part 8. Lecture at the Chemiedozententagung in Berlin, April 1978. – Part 7: *R. Mengel, W. Guschlbauer*, Angew. Chem. *90*, 557 (1978); Angew. Chem. Int. Ed. Engl. *17*, 525 (1978).

We have now investigated the reaction of TPA with compounds containing several hydroxyl groups in various configurations and of differing functionality; for example, the 9-(β-D-furanosyl)adenine derivatives *(1)*, *(3)*, *(5)*, and *(7)*.

According to *Mitsunobu*, reaction of adenosine *(1)* with TPA affords a 3′,5′-phosphorane[4e]. This structure is consistent with molecular models, and reactions with benzoic acid and thiobenzoic acid, which lead to the 5′-*O*-acyl derivatives.

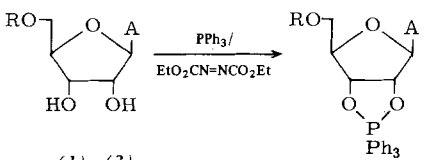
We have repeated the reaction of *(1)* with TPA and confirmed the previously quoted melting point of the product[5]. However, the NMR spectroscopic data favor the 2′,3′-phosphorane structure *(2)*:

a) The ^{1}H-NMR spectrum ([D$_6$]DMSO) shows a triplet at $\delta = 5.2$, which merges to a broad singlet on irradiation of the mean H$^{5'a}$, H$^{5'b}$ frequency and disappears on addition of D_2O.

b) In the ^{31}P-NMR spectrum ([D$_6$]DMSO) a signal is observed at $\delta = +26.6$ (standard: 85 % phosphoric acid), which lies in the region characteristic for triphenylphosphoranes.

c) Decoupling experiments reveal P—H coupling with H$^{2'}$ and H$^{3'}$, but not with H$^{5'a}$ or H$^{5'b}$.

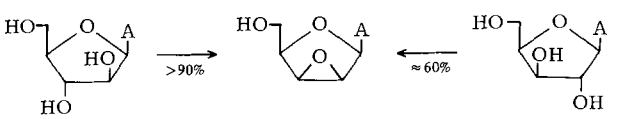
d) The phosphorane *(2)* can be acylated with benzoyl chloride/pyridine to 5′-*O*-benzoyladenosine *(3)*, which reacts with TPA to give the phosphorane *(4)* (^{31}P-NMR: $\delta = +26.5$).



(1), *(3)* *(2)*, *(4)*

(1), *(2)*: R = H; *(3)*, *(4)*: R = PhCO; A = Adenyl

The question now was how do the furanosyl derivatives of adenine containing *trans* hydroxyl groups react? Reaction of 9-(β-D-arabinofuranosyl)adenine *(5)* with TPA for 40 min at 70 °C affords the epoxide *(6)* in almost quantitative yield[5]. This constitutes the simplest route to this epoxide[6a], whose ring-opening affords biochemically interesting derivatives[6b] and whose previous syntheses involved several steps. On the other hand, reaction of 9-(β-D-xylofuranosyl)adenine *(7)* with TPA also yields *(6)*; however, a much longer reaction time (6 hours) is required.



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

The above results have been confirmed in the case of *cis*- and *trans*-cyclohexanediols. On reaction with TPA, the *trans* isomer affords cyclohexane epoxide; the ^{31}P-NMR spectrum gave no indication of the presence of an intermediate. *Mitsunobu* likewise obtained the epoxide, though in this case the reaction was carried out in the presence of benzoic acid (2 h, room temperature)[4a]. *Zbiral* and *Loibner* carried out the reaction in the presence of *p*-nitrobenzoic acid and isolated *trans*-2-hydroxycyclohexyl-*p*-nitrobenzoate[3a]. This finding is also reconcilable with an epoxide as intermediate which undergoes ring-opening under the reaction conditions (14 h, reflux).

In the reaction of *cis*-cyclohexanediol with TPA we could demonstrate by means of the ^{31}P-NMR spectrum that the phosphorane postulated by *Mitsunobu* is in fact formed: $\delta = +39$ ppm (standard: 85 % phosphoric acid).

Procedure

Reaction of *(1)*, *(3)*, *(5)*, and *(7)* with TPA: A mixture of the nucleoside and 1.5 equivalents of triphenylphosphane in anhydrous dioxane is stirred for 10 min at 70 °C under N_2. Diethyl azodicarboxylate (1.5 equivalents) diluted with dioxane is then added dropwise and the mixture stirred for a further 40 min at 70 °C.

Workup of *(2)*: After cooling, the reaction product is separated on a glass frit under N_2, washed with a few milliliters of dioxane, and finally recrystallized from dioxane under N_2 (yield: 78 %).

Synthesis of *(3)*: *(2)* (0.53 g, 1 mmol) is dissolved in anhydrous pyridine (30 ml) under N_2. The solution is treated dropwise with 0.135 ml (1.15 mmol) benzoyl chloride, stirred for 60 min at room temperature, and then poured over 300 g ice. The resulting ice-cold solution is extracted with ethyl acetate (3 × 50 ml) and the combined organic phases dried over Na_2SO_4 and finally evaporated down. The residue is then purified by preparative thin-layer chromatography (silica gel plates 20 × 40 × 0.2 cm, eluent chloroform/methanol 4:1). Yield of *(3)*: 0.27 g (72 %).

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CAS Registry numbers:
(1), 58-61-7; *(2)*, 67523-53-9; *(3)*, 15262-12-1; *(4)*, 67523-54-0; *(5)*, 5536-17-4; *(6)*, 40110-98-3; *(7)*, 524-69-6

[1] *O. Mitsunobu, M. Yamada*, Bull. Chem. Soc. Jpn. *40*, 2380 (1967).
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[5] CHN analysis gave the correct values.
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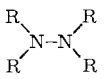
Synthesis and Conformation of 1,1′-Biazetidinyl

By *Karl Kirste, Wolfgang Lüttke*, and *Paul Rademacher*[*]

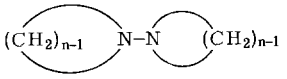
Hydrazine *(1)* and acyclic organic hydrazines have been shown to exist in the *gauche* form. This also applies for the unstrained 1,1′-bipiperidyl *(3d)*, whose conformation[1] corresponds to that of the tetramethylhydrazine *(2)*. For gaseous 1,1′-bipyrrolidinyl *(3c)* a mixture of *s-trans/gauche* conformers has been detected[1]. In contrast 1,1′-biaziridinyl *(3a)* assumes the *s-trans* conformation in all three aggregate states[2].

In order to examine how the conformation of the hydrazines *(3)* depends upon their ring size we synthesized the previously unknown 1,1-biazetidinyl *(3b)* and subjected it to a conformational analysis.

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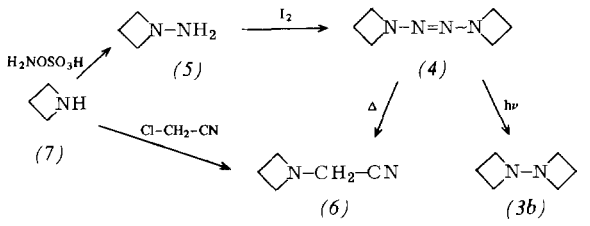


(1), R = H
(2), R = CH_3



(3a), n = 3; *(3b)*, n = 4
(3c), n = 5; *(3d)*, n = 6

All attempts to synthesize *(3b)* in an analogous way to *(3a)* and *(3c)* or *(3d)* met without success, but we were able to prepare it by photolysis of bis(trimethylene)tetrazene *(4)* in a steady state system in the gas phase[3]. *(4)* itself was prepared by gentle oxidation of 1-aminoazetidine *(5)*. Thus, an aminoazetidine was oxidatively dimerized for the first time, avoiding the nitrogen cleavage[4] otherwise observed. Pyrolysis of *(4)* in a dynamic gas-phase system at 300 °C did not lead to *(3b)*, but in 39 % yield to (1-azetidinyl)acetonitrile *(6)*, whose structure could be confirmed by an independent synthesis from azetidine *(7)* and chloroacetonitrile.



To determine the conformation of *(3b)* we recorded an IR spectrum of the liquid phase and Raman spectra of the liquid and solid (−100 °C) phases. For the centrosymmetric *s-trans* conformation with C_{2h} symmetry, 27 Raman and 27 IR lines without frequency-coincidence are to be expected; for all *gauche* forms with C_2 symmetry, 54 IR and 54 Raman lines with frequency-coincidence are to be expected.

The Raman spectrum of crystalline *(3b)* shows the requisite 27 lines for the *s-trans* form. Comparison of the IR and Raman spectra of liquid *(3b)* also demonstrates the validity of the exclusion rule for this conformation. This finding was supported by assignment of the vibrational spectra of *(3b)*, which correlated with those of *(4)* and *(7)*[3].

The Raman spectrum of liquid *(3b)* contains 17 additional lines, all of which coincide with IR bands of the liquid. It thus follows that a further conformer is present in the liquid phase in addition to the *s-trans* conformer. From the intensities of the lines it can be estimated that the *s-trans* form predominates.

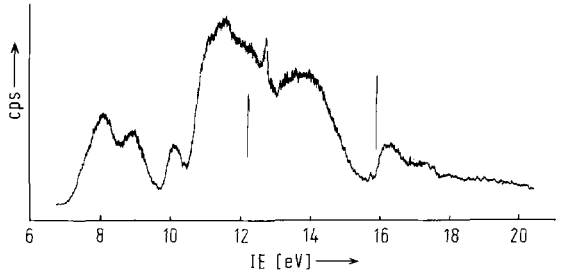


Fig. 1. PE spectrum of *(3b)*. The spectrum was recorded with a high-resolution photoelectron spectrometer (Model PS 16, Perkin-Elmer Ltd., Beaconsfield England; radiation source: He-I lamp, 21.22 eV).

We have been able to infer the conformation of gaseous *(3b)* from its PE spectrum (Fig. 1). In the region below 11 eV there appear three bands and a shoulder which can be ascribed to the ionization of electrons from the orbitals of the lone pair. The number of bands proves that two conformers are present[5], and their splitting patterns indicate, with the aid of a well-substantiated relationship between ionization potentials and dihedral angles of hydrazines[6], that they are the *s-trans*- ($\varphi = 180°$) and *gauche* conformers ($\varphi = 64°$). The splitting of 2.35 eV found for the *s-trans* form is only slightly smaller than that in *(3a)*.

Not only is twisting about the central N—N bond possible in *(3b)*, but also folding of the four-membered rings, leading to three inversion isomers analogously as in the isoelectronic hydrocarbon biscyclobutyl[7]. As yet we can only rule out the non-centrosymmetric *s-trans* inversion isomer in the solid phase.

In the case of *(3b)* all the hydrazines of type *(3)* with $n = 3$ to 6 have so far been demonstrated. Investigations have shown that the transition from the *s-trans* to the *gauche* form continuously takes place in the series *(3a)*, *(3b)*, *(3c)*, *(3d)*. Even highly strained compounds such as *(3b)* have a strong tendency to assume the *gauche* form.

Procedure

1-Aminoazetidine *(5)*: A solution of hydroxylamine *O*-sulfonic acid (22.6 g, 0.2 mol) in water (100 ml) is added dropwise at 0 °C to a stirred solution of *(7)* (57 g, 1 mol) and NaOH (40 g) in 400 ml water. After 1 h, three further portions of NaOH (each of 40 g) are added to the mixture. The organic phase is separated off and treated with powdered KOH until no water can be detected NMR spectroscopically. Fractional distillation (25 °C/22 torr) yields 6.9 g (26 %) *(5)*.

Bis(trimethylene)tetrazene *(4)*: To an ice-cooled solution of 0.66 ml conc. HCl and 0.5 g starch in 400 ml water under nitrogen is added 0.5 g (7 mmol) *(5)* and then 0.12 mol $Mg(OH)_2$. The mixture is titrated with a solution of 1.94 g (15.3 mmol) iodine and 5 g KI in 150 ml water. As soon as the end point is reached the solution is rendered alkaline with a solution of 8 g NaOH and 0.2 g $Na_2S_2O_3$ in 40 ml water, extracted three times with 80 ml pentane, and the combined extracts distilled after drying over $MgSO_4$. A single redistillation affords 0.15 g (31 %) *(4)*.

1,1'-Biazetidinyl *(3b)*: 100 mg (0.7 mmol) *(4)* is transferred to a 250 ml round-bottom flask and heated in an air-bath to 95 °C. After two hours' irradiation with a high-pressure mercury-vapor lamp (Hanovia 679A36) the contents of the flask are carefully redistilled. Subsequent gas-chromatographic separation (OV-210 column temperature 150 °C) furnishes 17 mg (21 %) pure *(3b)*.

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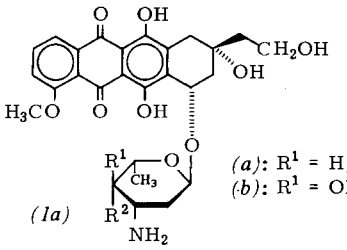
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(1), 302-01-2; *(2)*, 6415-12-9; *(3a)*, 67092-91-5; *(3b)*, 18389-95-2; *(3c)*, 6130-94-5; *(3d)*, 67523-79-9; *(4)*, 67523-80-2; *(5)*, 53779-89-8; *(6)*, 67523-81-3; *(7)*, 503-29-7; chloroacetonitrile, 107-14-2

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An Effective Synthetic Principle for Amino Sugars of the Daunosamine Type[**]

By *Ingolf Dyong* and *Reihard Wiemann*[*]

Daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) and its configurational isomers are of considerable interest as glycons of anthracyclines showing antineoplastic activity: among other things, adriamycin *(1a)* retains its antitumor activity on inversion at C-4 of the carbohydrate while almost completely losing its toxicity towards myocardial cells[1].



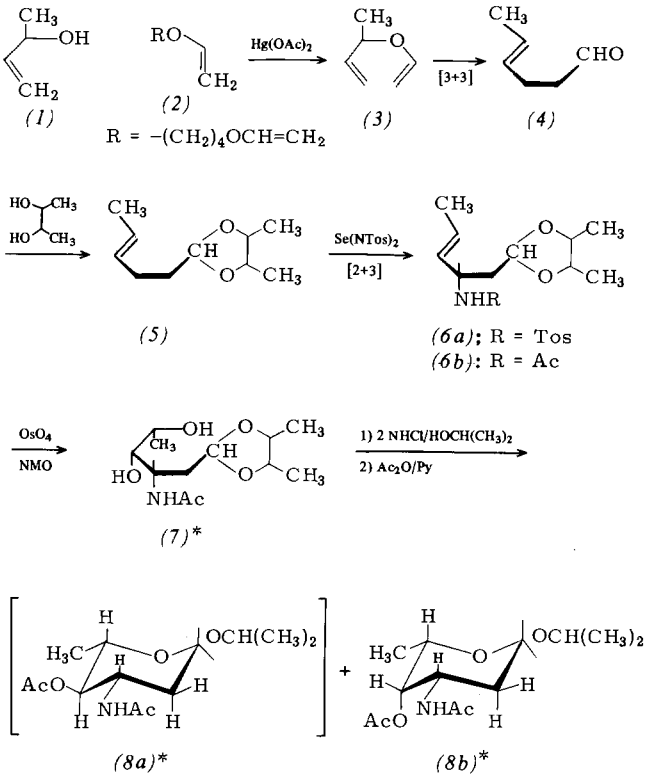
(1a)

(a): R^1 = H, R^2 = OH: Daunosamine (L-*lyxo*)
(b): R^1 = OH, R^2 = H: Acosamine (L-*arabino*)

Attempts to find powerful syntheses of daunosamine[2], acosamine[3a], ristosamine (L-*ribo*)[3b], and the *xylo* isomer so far leave much to be desired. Synthesis from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose[4] is currently regarded as the best entry to daunosamine. In order to produce antibiotic models of the daunomycin type we have sought a new route to daunosamine.

A combination of sigmatropic rearrangement of an allyl vinyl ether, allylic amination of the resulting 4-hexanal, and subsequent *cis*-hydroxylation proved to be a promising approach.

3-Buten-2-ol *(1)* reacts according to the transetherification procedure of *Watanabe* and *Conlon*[5] with 1,4-bis(vinyloxy)butane *(2)*/mercury acetate to give the allyl vinyl ether *(3)*[6]. Claisen rearrangement of this product gives the *trans*-4-hexenal *(4)*, which is allowed to react without isolation with *rac*-2,3-butanediol in the presence of *p*-toluenesulfonic acid to form the acetal *(5)*. The reaction sequence *(1)*→*(5)* (overall yield 65%) gives up to 70 g of *(5)*. Allylic amination of 10-g portions of the acetal *(5)* with selenium/chloramine T at room temperature in methylene chloride[7] leads to 4-tosylamino-DL-*glycero*-acetal *(6a)* (m.p. 70—72°C, yield 60%) along with a little of the 6-tosylamino derivative (*ca.* 10%). Removal of the toluenesulfonyl group with sodium in liquid ammonia and *N*-acetylation with acetic anhydride/methanol gives the 4-acetylamino-acetal *(6b)* (syrup, yield 80%). *cis*-Hydroxylation of *(6b)* with catalytic amounts of osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMO)[8] leads to a mixture of DL-*lyxo*/*xylo* configurated amino diols *(7)* (yield 96%), preferential formation of the *lyxo* isomer being expected for steric reasons. The protecting group in *(7)* can be removed with 2 N HCl. Removal of the acid by repeated evaporation with 2-propanol and acetylation afford the *N*,*O*-acetylated isopropyl glycoside *(8a, b)* (yield 70%), of which the DL-*lyxo* epimer (isopropyl 3-*N*-acetyl-4-*O*-acetyl-DL-daunosaminide) *(8b)* crystallizes immediately from ethyl acetate/light petroleum (m.p. 148—151°C; ^{1}H-NMR (100 MHz, $CDCl_3$): δ=4.99, dd (4-H), $^3J_{3',4'}$=4 Hz; δ=3.8, dq (5-H), $^3J_{4',5'}$=2 Hz[9]). The mass spectrometric fragmentation of *(8b)* corresponds to the pattern reported for methyl 3-*N*-acetyl-4-*O*-acetyl-L-daunosaminide by *Vigevani et al.*[10].



(1) *(2)* *(3)* *(4)* *(5)* *(6a)*; R = Tos *(6b)*: R = Ac *(7)**

*(8a)** *(8b)**

* Only the L forms are shown for *(7)* and *(8)*

Experiments using dimethyl L-(+)-tartrate as protecting group have shown that enantiomeric resolution is possible after allylic amination. However, acetalization proceeds better with 2,3-butanediol so that the reaction sequence *(3)*→*(7)* using optically active diols should provide the basis of a particularly effective synthesis of D- or L-daunosamine.

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CAS Registry numbers:
(1), 598-32-3; *(2)*, 3891-33-6; *(3)*, 3917-16-6; *(4)*, 25166-87-4; *(5)*, 67523-57-3; *(6a)*, 67530-60-3; *(6b)*, 67523-58-4; *(7)*, 67523-59-5; *(8b)*, 67523-60-8; *rac*-2,3-butanediol, 6982-25-8

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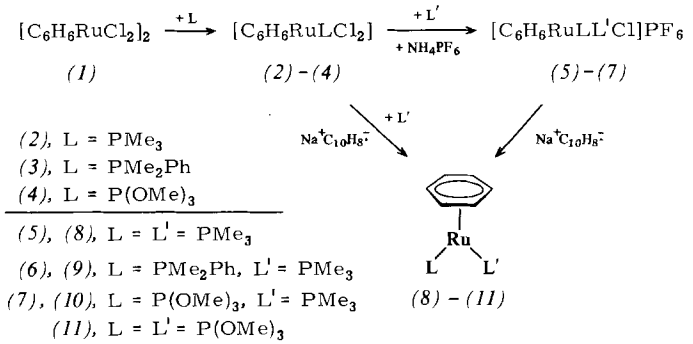
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[9] The ^{1}H-NMR data of *(8b)* agree with those of methyl 3-*N*-acetyl-4-*O*-acetyl-L-daunosaminide: cf. *F. Arcamone, G. Cassinelli, G. Franceschi, R. Mondelli, P. Orezzi, S. Penco*, Gazz. Chim. Ital. *100*, 949 (1970).
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A New Type of Ruthenium(0) Complex with a Half-Sandwich Structure: $C_6H_6RuL_2$[1]

By *Helmut Werner* and *Rainer Werner*[*]

Ruthenium(0) complexes of the type $C_6H_6RuL_2$ with L = CO, PR_3, $P(OR)_3$, *etc.*, were formerly unknown[2]. HMO calculations by *Albright* and *Hoffmann*[3] predict the bonding in $C_6H_6ML_2$ (M = Fe[4], Ru, Os) and $C_5H_5M'L_2$ (M' = Co, Rh, Ir) to be very similar. The cyclopentadienyl complexes $C_5H_5M'L_2$—and particularly those with L = PMe_3—are *strong Lewis bases*; they react with Lewis acids such as H^+, CH_3^+, CH_3CO^+, $ZnCl_2$, $HgCl_2$, $SnCl_4$, *etc.* extremely readily *via* addition and formation of stable M—H, M—C, or M-metal bonds[5].

We have now prepared benzeneruthenium(0) complexes with tertiary *phosphanes* and *phosphites* as ligands in a completely different way from that used in the synthesis of $C_5H_5M'(PMe_3)_2$ (M' = Co, Rh)[5] and $C_5H_5M'[P(OMe)_3]_2$ (M' = Co, Rh)[6]:



The successful synthesis of *(8)*—*(11)* depends upon the use of sodium dihydronaphthylide (in tetrahydrofuran) as reducing agent; it permits transformation of the readily accessible neutral compounds *(2)*—*(4)*, as well as the product cations $[C_6H_6RuLL'Cl]^+$, into the desired ruthenium(0) complexes.

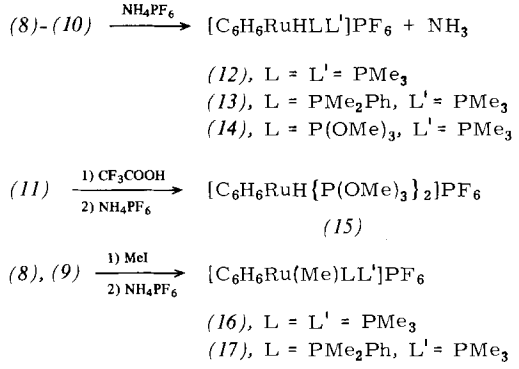
Compounds *(8)*—*(11)* are orange solids which melt at low temperatures; their ^{1}H-NMR data are compiled in Table 1. They are extremely sensitive to air and readily soluble in apolar (benzene, hexane) and in polar aprotic solvents (ether, THF).

Table 1. ^{1}H-NMR data of C_6H_6RuLL' *(8)*—*(11)* in C_6D_6 (δ values, rel. to int. TMS; J in Hz).

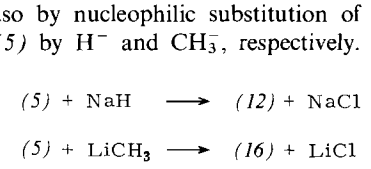
Com-plex	C_6H_6 [a]	L	L'
(8)	5.10 [J_{PH} = 1.1]	1.29 vt	(=L)
(9)	4.99 t [J_{PH} = $J_{P'H}$ = 1.1]	Me: 1.47 d [J_{PH} = 6.8] Ph: 7.0—7.5 m	1.01 d [J_{PH} = 7.6]
(10)	5.11 dd [J_{PH} = 0.75; $J_{P'H}$ = 1.1]	3.45 d [J_{PH} = 12.0]	1.25 d [J_{PH} = 8.2]
(11)	5.26 t [J_{PH} = 0.8]	3.47 vt	(=L)

[a] P = phosphorus atom of L, P' = phosphorus atom of L'.

The reactions of *(8)*—*(11)* with proton donors and methyl iodide confirm the strongly basic character of the central atom in C_6H_6RuLL'. While *(8)*, *(9)*, and *(10)* react with NH_4PF_6 to form the corresponding highly stable salts of the hydridoruthenium cations $[C_6H_6RuHLL']^+$ *(12)*—*(14)*, the formation of *(15)* from *(11)* requires the use of CF_3COOH. This provides a qualitative demonstration—as for the cyclopentadienyl complexes $C_5H_5M'L_2$—that the Lewis basicity of M in $C_6H_6ML_2$ (and C_6H_6MLL') is critically dependent upon the *donor/acceptor strength* of L (or L and L').



The preparation of *(12)* and *(16)* is possible not only starting from *(8)* but also by nucleophilic substitution of the chloride ligands in *(5)* by H^- and CH_3^-, respectively.



Compound *(12)* does not undergo elimination of H_2 to form *(8)* on treatment with an excess of NaH (in THF). On the contrary, the reaction of $[C_5H_5CoH(PMe_3)_2]PF_6$ with NaH yields the neutral complex $C_5H_5Co(PMe_3)_2$.

Procedure

Preparation of *(8)* from *(2)*: To a stirred suspension of *(2)* (0.5 mmol) in THF (2 ml) at −78 °C are simultaneously added dropwise PMe_3 (1 equiv.) and sodium dihydronaphthylide (2 equiv.), both as solutions in THF. The dark-brown reaction solution is evaporated to dryness at −20 °C, the residue is extracted with pentane (10 ml), and the pentane solution filtered through a cooled frit. Repeated fractional crystallization from pentane at −78 °C affords *(8)* as orange crystals (yield 70%). Compound *(11)* can be prepared from *(4)* (which like *(2)* is preparable from *(1)* and L in THF, 4 h, 50 °C) in analogous manner.

Preparation of *(8)* from *(5)*: To a stirred suspension of *(5)* (0.5 mmol) in THF (2 ml) at −78 °C is added sodium dihydronaphthylide (2 equiv.) as a solution in THF (2.5 ml). The reaction mixture is worked up as in the preparation of *(8)* from *(2)*. The synthesis of *(9)* from *(6)*, and that of *(10)* from *(7)*, can be accomplished in similar manner.

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(1), 37366-09-9; *(2)*, 67612-85-5; *(3)*, 39732-59-7; *(4)*, 35796-50-0; *(5)*, 67612-87-7; *(6)*, 67612-89-9; *(7)*, 67612-91-3; *(8)*, 67612-92-4; *(9)*, 67651-08-5; *(10)*, 67612-93-5; *(11)*, 67612-94-6; *(12)*, 67612-96-8; *(13)*, 67651-10-9; *(14)*, 67612-98-0; *(15)*, 67613-00-7; *(16)*, 67613-02-9; *(17)*, 67651-12-1

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[1] Basic Metals, Part 12. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and by gifts of chemicals from Bayer AG, Leverkusen, and Degussa, Hanau.—Part 11: *H. Werner, R. Feser, W. Buchner*, Chem. Ber., in press.

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[3] *T. A. Albright, R. Hoffmann*, unpublished results; cf. Chem. Ber. *111*, 1578 (1978).

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[5] a) M = Co: *H. Werner, W. Hofmann*, Chem. Ber. *110*, 3481 (1977); *K. Dey, H. Werner*, J. Organomet. Chem. *137*, C28 (1977); b) M = Rh: *R. Feser*, Diplomarbeit, Universität Würzburg 1977; cf. also [1].

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K_2Te_3: The First Binary Alkali-Metal Polytelluride with Te_3^{2-} Ions[**]

By *Brigitte Eisenmann* and *Herbert Schäfer*[*]

The only compound in the K/Te system to have been structurally characterized is K_2Te[1,2], although polytellurides were predicted some time ago by *Klemm et al.*[2] on the basis of magnetic studies performed on this system. While examining Zintl phases possessing aggregate anionic partial structures we have synthesized the compound K_2Te_3 from the elements and isolated it as single crystals. The compound crystallizes in the form of metallic gray prisms which are usually highly distorted.

The structure of this, the first binary alkali metal polytelluride was determined from four-circle diffractometer data obtained for a single-crystalline fragment (Stoe Stadi IV, $Mo_{K\alpha}$, 700 reflections, $R = 0.099$). K_2Te_3 forms orthorhombic crystals, space group Pnma with $a = 1593.8(5)$, $b = 1009.7(5)$, $c = 468.6(3)$ pm [K at 8*d* with $x = 0.3776(6)$, $y = 0.0303(13)$, $z = 0.2892(20)$; Te^1 at 4*c* with $x = 0.4815(2)$, $y = 1/4$, $z = 0.8152(7)$; Te^2 at 4*c* with $x = 0.2594(2)$, $y = 1/4$, $z = 0.7020(8)$; Te^3 at 4*c* with $x = 0.1223(2)$, $y = 1/4$, $z = 0.3267(7)$].

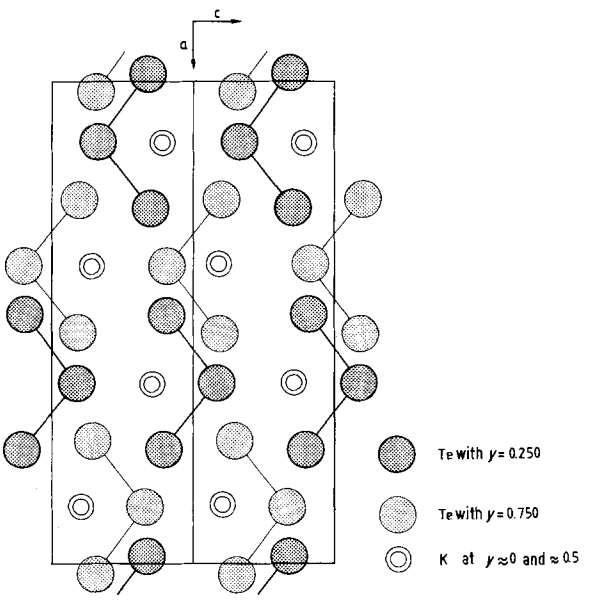


Fig. 1. Projection of atomic arrangement in K_2Te_3 onto the *a*, *c* plane.

The anionic components of this structure are bent Te_3 chain fragments (Fig. 1) arranged in planes $\perp b$ at $y = 0.25$ and $y = 0.75$. The Te—Te distances within such groups are 280.2 and 280.5 pm and are thus shorter than in α-tellurium 283.4 pm), while the bond angle is slightly greater than that in α-tellurium (103.2°). The closest contact between the Te atoms of neighboring Te_3 groups is 357.9 pm (the helical chains in α-tellurium are 349.4 pm apart). The K atoms have eight Te neighbors at distances of 349.5 to 400.6 pm; a strongly distorted four-sided antiprism is found as coordination polyhedron.

Comparison of the compound K_2Te_3 with the cryptate $(C_{18}H_{36}N_2O_6K)_2Te_3$[3] proves interesting. The latter also contains a bent Te_3^{2-} ion which, however, is far less symmetrical with regard to bond lengths. The existence and structure of K_2Te_3 demonstrate that polyanionic systems in the 6th Main Group are not limited to selenides and sulfides, and that the occurrence of Te_3^{2-} ions is not dependent upon the presence of cryptate cations as counterions.

Procedure

A stoichiometric mixture of potassium and tellurium was sealed in carefully baked out quartz ampoules in a dry, oxygen-free atmosphere. The ampoules were placed in iron tubes which were sealed by welding, slowly heated to *ca.* 600 °C within 4 h, and annealed at 250 °C for 12 h [analysis of selected single crystals: Te 82.9 (calc. 83.04) %; K 16.1 (calc. 16.96) %].

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K_2Te_3, 67488-76-0

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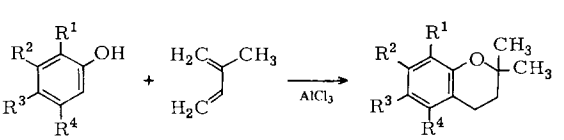
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Selectivity in Reactions between Metal Phenoxides and Isoprene. Facile Synthesis of 2,2-Dimethylchromans[**]

By *Luciana Bolzoni, Giovanni Casiraghi, Giuseppe Casnati*, and *Giovanni Sartori*[*]

Among the isoprenylating agents, isoprene is a simple, readily available and economic chemical; however, the regiochemical control in reactions involving phenol or its simple derivatives is still an unsolved problem[1,2]. By way of contrast we have found that direct chromanation of phenols *(1)* with isoprene under unusual Friedel-Crafts conditions provides



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Table 1. Synthesis of 2,2-dimethylchromans *(2)*. The structure of the chromans was confirmed by comparison with authentic materials or by spectroscopic findings.

	R^1	R^2	R^3	R^4	B.p. [°C/torr]	Yield [%] [a]	[b]	Lit. b.p. [°C/torr]
(a)	H	H	H	H	67—68/2	65	93	98.5/11.5 [4]
(b)	CH_3	H	H	H	70—72/2 [c]	55	91	[5]
(c)	H	H	CH_3	H	91—92/2 [c]	61	96	[5]
(d)	H	H	Cl	H	94—95/1 [d]	86	98	
(e)	H	OCH_3	H	H	100—101/1	56 [e]	90	102/1 [6]
(f)	H	OCH_3	H	OCH_3	110—112/1	40	95	114/1 [6]
(g)	H	OH	H	CH_3	140—143/2	51	93	138—139/1.5 [6]
(h)	CH_3	CH_3	OH	CH_3	m.p. 93—94°C	64	97	m.p. 93—94°C [2]

[a] Isolated yields, based on total amount of *(1)* employed. [b] Yield based on unrecovered *(1)*. [c] Lit. [5] b.p. values not reported. [d] Correct C, H, Cl analysis for $C_{11}H_{13}ClO$. [e] 5% of 5-methoxy-2,2-dimethylchroman also formed (b.p. 104—105°C/1 torr).

Table 2. Reaction of phenol-phenoxide-Lewis acid systems with isoprene under comparable conditions at 19±0.5°C.

No.	PhOH [mol]	PhOM M^+ [mol]	Lewis acid [mol]	Solvent Additive [a]	Conversion [%] [b]	*(2a)*, Yield [%] [b]
1	1.0	K^+ (1.0)	$AlCl_3$ (1.0)	Benzene	71	68
2	1.0	K^+ (1.0)	$FeCl_3$ (1.0)	Benzene	10	5
3	1.0	K^+ (1.0)	$SnCl_4$ (1.0)	Benzene	55	25
4	—	K^+ (1.0)	$AlCl_3$ (1.0)	Benzene	38	15
5	1.0	—	$AlCl_3$ (1.0)	Benzene	2.0	ND
6	1.0	K^+ (1.0)	—	Benzene	1.5	ND
7	1.0	Na^+ (1.0)	$AlCl_3$ (1.0)	Benzene	25	15
8	1.0	Li^+ (1.0)	$AlCl_3$ (1.0)	Benzene	40	22
9	1.0	Al^{3+} (0.3) [c]	$AlCl_3$ (1.0)	Benzene	46	30
10	1.0	K^+ (1.0)	$AlCl_3$ (1.0)	Ether	1.5	ND
11	1.0	K^+ (1.0)	$AlCl_3$ (1.0)	Benzene+TMEDA [d]	0.0	ND
12	1.0	K^+ (1.0)	$AlCl_3$ (1.0)	Benzene+Crown [d]	0.0	ND

[a] Ether = diethyl ether, TMEDA = tetramethylethylenediamine, Crown = Dibenzo[18]crown-6. [b] Determined by GLC analyses (Se 30, 5% on chromosorb W, *ca.* 3.2 mm × 2.4 m, 120°C). ND = Not detected. [c] 0.3 mol $(PhO)_3Al$. [d] 1 mole of additive per mole of PhOM.

a general highly selective synthesis of 2,2-dimethylchromans *(2)* (see Table 1). Thus, reaction of a 1:1:1 mixture of phenol, potassium phenoxide and $AlCl_3$ with isoprene in benzene at room temperature affords 2,2-dimethylchroman *(2a)* in 63—65% yield, along with trace amounts (<1%) of *p*-isopentenylphenol. Some 30% of phenol remains unreacted; other constituents of the product include *o*-isopentenylphenol (traces) and 6-isopentenyl-2,2-dimethylchroman (2–3%).

Iron(III) and tin(IV) chlorides are less effective catalysts than aluminum chloride (Table 2, No. 2 and 3). The optimum molar ratio of phenol to phenoxide and $AlCl_3$ is nearly 1:1:1. If one of these three reagents is removed, the yield is drastically reduced (Nos. 4—6). Furthermore, it is worth noting that the use of sodium, lithium, or aluminum phenoxides instead of potassium phenoxide causes a remarkable lack of specificity (Nos. 7—9). Finally, the reaction fails completely when ether solvents or cation coordinating or complexing additives are used (Nos. 10—12).

This is not the first example of variable orientation and dependence of yields upon reaction conditions in processes involving complexes between phenols and Lewis acids or metal phenoxides[7], but the latitude in the choice of substrate as well as the excellent substrate and positional selectivity make this reaction unique and capable of further development in its scope. For example, it has been used for the synthesis of 2-methyl-2-(4-methyl-3-pentenyl)chroman from phenol and myrcene; b.p. 90°C/0.01 torr (bulb-tube distillation), yield *ca.* 60%.

Procedure

A slurry of phenol *(1a)* (0.1 mol), potassium phenoxide (0.1 mol)[3] and $AlCl_3$ (0.1 mol) in benzene is refluxed with stirring for 10 min. The resulting colorless solution is cooled to/or below 20°C and a solution of isoprene (0.2 mol) in benzene is added at a uniform rate (*ca.* 0.04 mol h^{-1}). After the addition is complete, the mixture is allowed to stand, usually overnight, then diluted with a saturated NH_4Cl-water solution and extracted with ether. Solvent removal and chromatography of the residue on a short column of silica gel (100 g) with hexane affords *(2a)* in 63—65% yield (90—93% based on unrecovered phenol).—This procedure is of wide applicability and can be extended without modification to a variety of substituted mono and polyhydric phenols.

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CAS Registry numbers:
(1a), 108-95-2; *(1b)*, 95-48-7; *(1c)*, 106-44-5; *(1d)*, 106-48-9; *(1e)*, 150-19-6; *(1f)*, 500-99-2; *(1g)*, 504-15-4; *(1h)*, 700-13-0; *(2a)*, 1198-96-5; *(2b)*, 23446-51-7; *(2c)*, 23446-57-3; *(2d)*, 67523-55-1; *(2e)*, 20052-58-8; *(2f)*, 67523-56-2; *(2g)*, 1746-16-3; *(2h)*, 950-99-2; isoprene, 78-79-5

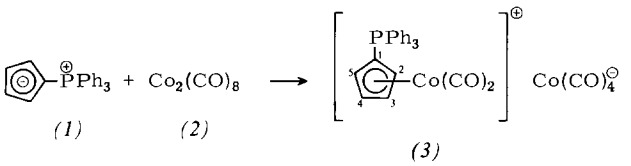
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Synthesis and Structure of the Ylide Complex $[(Ph_3P{-}C_5H_4)Co(CO)_2]^+[Co(CO)_4]^-$. Its Use in the Cyclotrimerization of Alkynes[**]

By *Norman L. Holy, Norman C. Baenziger*, and *R. M. Flynn*[*]

We wish to report the formation of a new[1] ylide metal-carbonyl complex *(3)* formed by combining octacarbonyldicobalt *(2)* with triphenylphosphoniocyclopentadienide *(1)* in tetrahydrofuran, under nitrogen (see *Experimental*). The complex *(3)* was characterized by a crystallographic structure analysis as $[(Ph_3P{-}C_5H_4)Co(CO)_2]^+[Co(CO)_4]^-$ [2].



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

The anion $[Co(CO)_4]^-$ is a nearly regular tetrahedron, with bond angles ranging from 107.0(3)° to 112.6(3)° (average 109.5°). The Co—C_{CO} distances are 1.751(7), 1.756(9), 1.752(8), and 1.746(8) Å. The cation (Figure 1) has a π bonded ylide

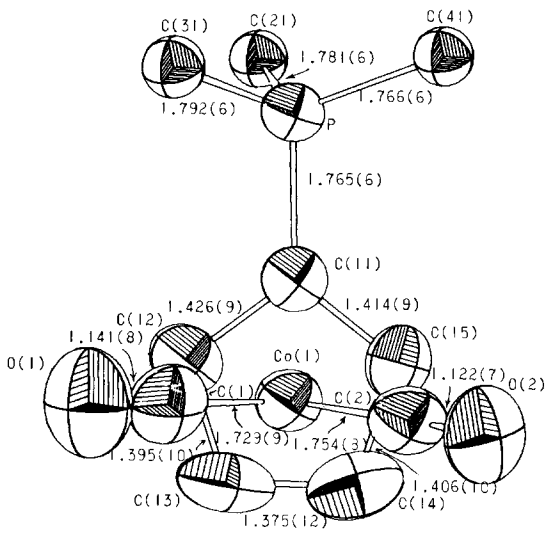


Fig. 1. Structure of the cation $[(Ph_3P{-}C_5H_4)Co(CO)_2]^+$ (ORTEP diagram).

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group and two carbonyl groups attached to the Co atom; Co—C_{CO} = 1.729(9), 1.754(8) Å; OC—Co—CO angle = 94.5(3)°. The C—C distances in the cyclopentadienide ring are not significantly changed from those in the uncomplexed ylide *(1)*. In contrast, the P—C^1 bond is significantly longer than in *(1)*. The Co—Co distance is 5.231 Å, and there are no groups bridging the two cobalt atoms. The structure of *(3)* bears similarity to that reported recently for $(Me_2S{-}C_5H_4Cr(CO)_3$ [3].

Because of the analogy of the isolated salt *(3)* to $CpCo(CO)_2$, we wished to establish if there were chemical similarities between the two complexes; this was tested by determining whether *(3)* would cyclotrimerize alkynes[4]. We found that 4-octyne was converted into hexa-*n*-propylbenzene, both by *(3)* (see *Experimental*) and by *(3)* generated *in situ* [*(1)* + *(2)*, 30 minutes' stirring, addition of 4-octyne]. Tolane was converted into hexaphenylbenzene in 96 % yield; no other tolane-derived products were detected.

Experimental

Synthesis of *(3)*: All steps must be carried out in a drybox; the THF and petroleum ether should not contain water or dissolved oxygen.—To a solution of 1.63 g (5.0 mmol) of *(1)* in 200 ml of dry, deoxygenated THF was added 1.50 g (4.4 mmol) of *(2)*. A deep-red color formed immediately and bubbles were evolved. After stirring at room temperature for 0.5 h, dry, deoxygenated petroleum ether was added to precipitate out 1.73 g (65 %) of yellow-red crystals, m. p. 110—115 °C. After recrystallization three times from THF-petroleum ether, 0.84 g of *(3)* was recovered as yellow crystals having m. p. 120—122 °C; IR (KBr): 2109, 2082, 1890 cm^{-1}.

Cyclotrimerization: To a solution of 0.628 g (1.00 mmol) of *(3)* in 25 ml of dry, deoxygenated THF was added 3.30 g (30.0 mmol) of 4-octyne. After refluxing under nitrogen for three days the solvent was stripped off and the products were chromatographed on a neutral alumina column (2 cm × 35 cm). 2.08 g (63 %) hexa-*n*-propylbenzene, m. p. 94—98 °C, was eluted with petroleum ether. No other octyne-derived products were found, though other products are present—68 % of the alkyne is converted. After recrystallization from benzene the melting point of the cyclotrimerization product increased to 100—101 °C.

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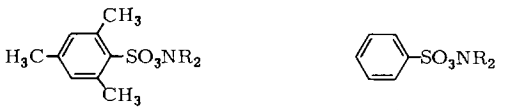
CAS Registry numbers:
(1) (charged form), 29473-30-1; *(1)*, 2224-32-0; *(2)*, 10210-68-1; *(3)*, 67505-81-1; 4-octyne, 1942-45-6; hexa-*n*-propylbenzene, 2456-68-0

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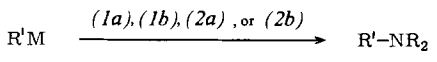
Electrophilic Amination of "Carbanions" with *N,N*-Dialkyl-*O*-arylsulfonylhydroxylamines[**][1]

By *Gernot Boche, Nava Mayer, Michael Bernheim,* and *Konrad Wagner*[*]

Although there are numerous examples for the amination of nucleophiles with X—NR_2 (X = anionic leaving group, R = H)[2], only isolated reports have been published about the reaction of "carbanions" (more precisely organometallic compounds R'M)[3]. We have performed a study of the electrophilic amination of R'M *(3)* with the *N,N*-dialkyl-*O*-arylsulfonylhydroxylamines *(1a)*, *(1b)*, *(2a)*, and *(2b)* to form the tertiary amines *(4)* (see Table 1).



(1a), R = CH_3; *(1b)*, R = C_2H_5 *(2a)*, R = CH_3; *(2b)*, R = C_2H_5



(3) *(4)*

The amination reagents *(1a)*, *(1b)*, *(2a)*, and *(2b)* were synthesized in 60—90% yield by reaction of the corresponding arylsulfonyl chloride with the corresponding dimethyl- or diethyl-hydroxylamine (or hydroxylamine hydrochloride) and triethylamine in dichloromethane at −20 to −10°C[4]. No differences in amination readiness could be detected between *(1a)*, *(1b)*, *(2a)*, and *(2b)*.

We gave preference to the synthesis of amines *(4)* which are accessible only under drastic conditions, if at all, by nucleophilic substitution [*(4cb)*, *(4da)*, *(4fa)*, *(4ga)*, *(4la)*] and whose organometallic precursors R'M *(3)* are relatively easy to obtain and "stable". Amines of bicyclo[1.1.0]butanes were hitherto inaccessible, even by degradation reactions. Reaction *(3g)* → *(4ga)* opens up a general route to amines of strained ring systems.

Procedures

N,N-Dimethyl-*O*-mesitylsulfonylhydroxylamine *(1a)*: *N,N*-Dimethylhydroxylamine hydrochloride (5.0 g, 51 mmol) is suspended in CH_2Cl_2 (40 ml) at −10°C. Triethylamine (11 g, 110 mmol) is added with stirring, followed, over a period of 90 min, by a solution of mesitylsulfonyl chloride (9.8 g, 45 mmol) in CH_2Cl_2 (40 ml). After another hour at −10°C, the reaction mixture is shaken with ice-water (100 ml), the organic phase separated off, and the aqueous phase washed with ether (2 × 50 ml). After drying the ether phase with $MgSO_4$ and removal of solvent under reduced pressure at 0°C compound *(1a)* precipitates as colorless crystals. Recrystallization from ether leads to 9.3 g (85%) of *(1a)*, m.p. 101—102°C, ^{1}H-NMR ($CDCl_3$): δ = 2.28 (s; *p*-CH_3), 2.60 (s; *o*-CH_3 and NMe_2), 6.87 (s; *m*-H).

N,N-Dimethyl-*cis,trans*-2,3-diphenylcyclopropylamine *(4fa)*: An ether solution of *(3f)* (70 ml, 6.1 mmol) is added at −10°C to a suspension of *(1a)* (1.50 g, 6.1 mmol) in THF (20 ml); the mixture is allowed to warm to 25°C and stirred for 15 h. Workup as usual for amines (2 N HCl, 2 N NaOH) and recrystallization from ether/pentane affords *(4fa)* (790 mg, 47%) as colorless crystals (m.p. 66—68°C).

Table 1. Synthesis of tertiary amines *(4)* by electrophilic amination of the "carbanions" *(3)* at −20 to +20°C in ether or ether/THF.

(3)	R'M	Aminating reagent	*(4)*	Detection as	by [a]	M.p. [°C]	Yield [%]
(3a)	Methyllithium	*(1a)*	*(4aa)*	*(4aa)*·MeI	a. s.		45
		(2b)	*(4ab)*	*(4ab)*·MeI	a. s.		39
(3b)	*n*-Butyllithium	*(1a)*, *(2a)*	*(4ba)*	*(4ba)*·MeI	a. s.		47
(3c)	Phenylmagnesium bromide	*(1b)*	*(4cb)*	*(4cb)*	a. s.		42
(3d)	1-Naphthyllithium	*(1a)*, *(2a)*	*(4da)*	*(4da)*	a. s.		9
(3e)	1-Naphthylmagnesium bromide		*(4ea)*	*(4ea)*	a. s.		69
(3f)	*cis,trans*-2,3-Diphenylcyclopropylmagnesium bromide	*(1a)*	*(4fa)*	*(4fa)*	anal.	66—68	47
(3g)	Tricyclo[4.1.0.0^{2,7}]hept-1-yllithium	*(1a)*	*(4ga)*	*(4ga)*	a. s., MS [b]		54
(3h)	(*Z*)-1-Propenyllithium	*(1b)*	*(4hb)*	*(4hb)*	a. s. [5]		28
(3i)	1,2,3-Triphenylallyllithium	*(1a)*	*(4ia)*	*(4ia)*-picrate	anal.	167—168	38
		(1b)	*(4ib)*	*(4ib)*-picrate	anal., MS	133—134	39
(3j)	1,3-Diphenylallyllithium	*(1a)*	*(4ja)*	*(4ja)*-picrate	anal.	173—174	37
(3k)	1,3-Diphenyl-2-*tert*-butylallyllithium	*(1a)*	*(4ka)*	*(4ka)*-picrate	anal.	173—174	31
(3l)	Cyclononatetraenyllithium	*(1a)*	*(4la)* → *(5)* [c]	*(4la)* → *(5)* [c]	a. s. [6]		69
(3m)	Indenyllithium	*(1a)*	*(4ma)* + *(4ma)'* [d]	*(4ma)* / *(4ma)'*	a. s. [e]		57
(3n)	Fluorenyllithium	*(1a)*	*(4na)* [f]	*(4na)*-picrate	a. s. [7]	202—203	61
(3o)	Ethyl-2-lithiophenylcyanoacetate	*(1a)*	*(4oa)*	*(4oa)*	anal., MS		95

[a] a. s. = authentic sample, anal. = elemental analysis, MS = mass spectrometry; all amines were detected by ^{1}H-NMR spectroscopy. [b] The synthesis of *(4ga)*, which is very sensitive to electrophiles (*e.g.* $H^{\oplus}$ and O_2), was confirmed by an independent route; *G. Szeimies*, Universität München, personal communication. [c] *(4la)* = *N,N*-dimethyl-2,4,6,8-cyclononatetraenylamine; *(5)* = *N,N*-dimethyl-3a,7a-dihydro-1*H*-1-indenylamine. [d] *(4ma)* = *N,N*-dimethyl-1*H*-1-indenylamine; *(4ma)'* = *N,N*-dimethyl-1*H*-3-indenylamine. [e] Reaction of *(4ma)* + *(4ma)'* with CH_3I affords an analytically pure ammonium iodide, m.p. 145—146°C (dec.). [f] *N,N*-Dimethyl-9-fluorenylamine.

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(1a), 67530-30-7; *(1b)*, 67530-31-8; *(2a)*, 67530-32-9; *(2b)*, 67530-33-0; *(3a)*, 917-54-4; *(3b)*, 109-72-8; *(3c)*, 108-86-1; *(3d)*, 14474-59-0; *(3e)*, 98-11-9; *(3f)*, 61608-79-5; *(3g)*, 66464-70-8; *(3h)*, 6524-17-0; *(3i)*, 58378-29-3; *(3j)*, 34631-38-4; *(3k)*, 67530-34-1; *(3l)*, 875-01-4; *(3m)*, 20669-47-0; *(3n)*, 881-04-9; *(3o)*, 67556-06-3; *(4aa)*·MeI, 75-58-1; *(4ab)*·MeI, 4325-24-0; *(4ba)*·MeI, 7722-19-2; *(4cb)*, 91-66-7; *(4da)*, 86-56-6; *(4fa)*, 67530-35-2; *(4ga)*, 67530-36-3; *(4hb)*, 13044-39-8; *(4ia)* picrate, 67530-38-5; *(4ib)* picrate, 67530-40-9; *(4ja)* picrate, 19969-93-8; *(4ka)* picrate, 67530-42-1; *(4la)*, 67530-43-2; *(4ma)*, 67530-44-3; *(4ma)'*,

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28003-01-2; *(4na)* picrate, 67530-45-4; *(4oa)*, 67530-46-5; *(5)*, 67556-05-2; *N,N,N*-trimethyl-1*H*-indenaminium iodide, 67523-66-4; *N,N*-dimethylhydroxylamine HCl, 16645-06-0; mesitylsulfonylchloride, 773-64-8; benzenesulfonylchloride, 98-09-9

[1] From the Diploma Theses of *N. Mayer* and *M. Bernheim*, Universität München 1977 and 1978, respectively.

[2] Reviews: *E. Schmitz*, Usp. Khim. *45*, 54 (1976); *Y. Tamura, J. Minamikawa, M. Ikeda*, Synthesis *1977*, 1.

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[4] *(1a)*, m.p. 101—102°C (dec.); *(1b)*, m.p. 68—69°C (dec.); *(2a)*, m.p. −3 to 0°C (dec.); *(2b)*, m.p. 50—51°C (dec.). After recrystallization from ether *(1a)* and *(1b)* can be kept indefinitely, and *(2a)* and *(2b)* for several weeks, in a refrigerator. Explosions occurring with anhydrous *(1)*, R=H (see *R. Y. Ning*, Chem. Eng. News *51*, (Dec. 17), p. 37 (1973)) were not observed.

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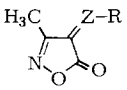
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Synthesis of Aryl and Heteroaryl Isocyanides from Nitroso Compounds[**]

By *Curt Wentrup, Uschi Stutz*, and *Hans-Joachim Wollweber*[*]

We recently described the synthesis of aryl- and heteroarylacetylenes *(2)*[1] by thermal decomposition of 4-arylmethylideneisoxazol-5(4*H*)-ones *(1a)*, as well as the generation and rearrangement of isocyanoamines *(3)*[2] from the correspond-



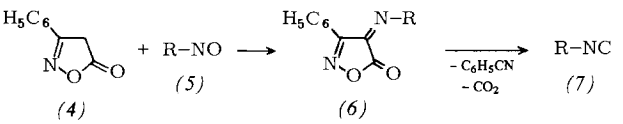
(1a), Z = CH
(1b), Z = NNH

R–C≡CH *(2)*

R–NH–NC *(3)*

ing hydrazones *(1b)*. We now wish to report a preparation of hitherto unknown classes of heteroaryl isocyanides, which is useful also for the production of otherwise difficultly accessible aryl isocyanides.

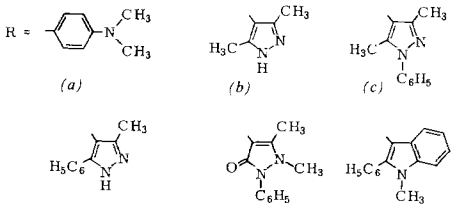
3-Phenyl-4-(*p*-dimethylaminophenyl)iminoisoxazol-5(4*H*)-one *(6a)* is readily obtained by condensation of *N,N*-dimethyl-4-nitrosoaniline *(5a)* with 3-phenylisoxazol-5(4*H*)-one *(4)* in ethanol solution[3]. *(6a)* decomposes at its melting point (165°C) with formation of benzonitrile, CO_2, and 4-isocyano-*N,N*-dimethylaniline *(7a)*. The isocyanide *(7a)* is obtained



(4) + R–NO *(5)* → *(6)* → (−C_6H_5CN, −CO_2) R–NC *(7)*

in near-quantitative yield when *(6a)* is allowed to decompose in a sublimation apparatus under high vacuum at 130—140°C, or by gas-phase pyrolysis of *(6a)* at 150°C. For preparative purposes, *(6a)* is conveniently decomposed in toluene solution at 90°C (30 h). Distillation of the solvent and benzonitrile, and sublimation of the residue at 60°C *in vacuo* affords the isocyanide *(7a)* in analytical purity[4] and 94% yield (see Table 1) [^{1}H-NMR ($CDCl_3$): $\delta = 2.9$ (s, 6H), 6.6 (d, $J = 9$ Hz, 2H), 7.2 (d, $J = 9$ Hz, 2H)].

Table 1. 4-Iminoisoxazolones *(6)* and isocyanides *(7)*.



(a) *(b)* *(c)* *(d)* *(e)* *(f)*

Cmpd.	*(6)* Yield [%] [a]	*(6)* M.p. [°C]	*(6)* *T* [°C] [b]	*(7)* Yield [%]	*(7)* M.p. [°C]	ν_{NC} [cm^{-1}]
a	80	165	90	94	60	2120
b	62	140	100	95	135	2120
c	60	161	110	97	67	2130
d	40	101	95	95	130—132	2130
e	86	153—155	100	92	178	2120
f	54	155	100	92	99	2120

[a] Based on nitroso compound *(5)*.
[b] Decomposition of *(6)* in toluene solution.

(7a) was previously known[5,6] only in admixture with the isomeric nitrile *(8a)*, and it was stated[5] that *(7a)* was so unstable that it could only be identified by infrared spectroscopy. Quite on the contrary, we find that *(7a)* is thermally stable. Gas-phase pyrolysis above *ca.* 350°C forms a mixture of *(7a)* and *(8a)*, and at 800°C only the nitrile *(8a)* is obtained.

R–NC $\xrightarrow{\Delta}$ R–CN
(7) *(8)*

In a similar manner, the pyrazole and indole derivatives *(6b)*—*(6f)* decompose in toluene solution with formation of the corresponding isocyanides *(7b)*—*(7f)* in yields over 90% (Table 1)[4]. Gas-phase pyrolysis above *ca.* 500°C affords the isomeric nitriles *(8b)*—*(8f)*. Compounds *(7b)*—*(7f)* are the first reported isocyanides of the pyrazole and indole series. Indeed, heterocyclic chemistry is almost devoid of isocyanides[7]. Thus, the high yields and the extremely simple experimental procedure endows the present method with considerable scope as a synthesis of aryl- and heteroaryl isocyanides, as well as the isomeric nitriles.

Experimental

Synthesis of *(6f)*: A suspension of 1-methyl-3-nitroso-2-phenylindole *(5f)* (0.75 g, 3.2 mmol) in ethanol (40 ml) was added to a warm, saturated solution of *(4)* (0.52 g, 3.2 mmol) in ethanol (25 ml). After addition of three drops of piperidine the color of the solution changed from green to red-violet. The mixture was heated for 15 min on a water-bath, and then allowed to crystallize at 0°C. The dark brown-violet crystals of *(6f)* were recrystallized from ethanol/benzene (1 : 1); yield 0.645 g.

Synthesis of *(7f)*: A solution of *(6f)* (100 mg, 0.26 mmol) in toluene (30 ml) was heated at 100°C for 20 h. The solvent

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and benzonitrile were removed *in vacuo*, and the residue sublimed at 80—85 °C/0.01 torr, yielding 56 mg of *(7f)* [^{1}H-NMR (CCl_4/$CDCl_3$ 10:1): $\delta = 3.66$ (s, 3H), 7.2—7.7 (m, 9H)].

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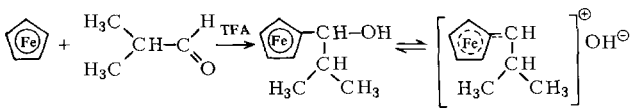
CAS Registry numbers:
(4), 1076-59-1; *(5a)*, 138-89-6; *(5b)*, 1122-04-9; *(5c)*, 715-99-1; *(5d)*, 27318-25-8; *(5e)*, 885-11-0; *(5f)*, 53603-63-7; *(6a)*, 67523-67-5; *(6b)*, 67523-68-6; *(6c)*, 67523-69-7; *(6d)*, 67523-70-0; *(6e)*, 67523-71-1; *(6f)*, 67523-72-2; *(7a)*, 7050-85-3; *(7b)*, 67523-73-3; *(7c)*, 67523-74-4; *(7d)*, 67523-75-5; *(7e)*, 67523-76-6; *(7f)*, 67523-77-7

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Direct Formation of the α-Ferrocenylisobutyl Cation from Ferrocene and Isobutyraldehyde[**]

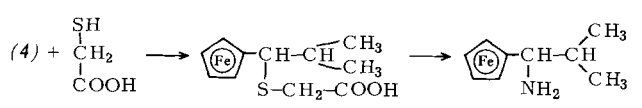
By *Rudolf Herrmann* and *Ivar Ugi*[*]

We suspected that ferrocene *(1)* can undergo electrophilic substitution by isobutyraldehyde *(2)* in trifluoroacetic acid (TFA) to form *(3)*, which equilibrates with *(4)*. Evidence favoring this idea comes from (a) the formation of highly stable α-ferrocenylalkyl cations from α-ferrocenylalkanols in TFA[1], (b) the enhancement of electrophilic reactivity of carbonyl compounds by *O*-protonation[2], and (c) the role played by the α-ferrocenylisobutyl cation *(4)*[4] in the chemistry of α-ferrocenylisobutylamine *(7)*[3]. Compound *(7)* is the asymmetrically inducing chiral reference system for peptide syntheses by stereoselective four-component condensation[4].



(1) *(2)* *(3)* *(4)*

Joint dissolution of *(1)* and *(2)* in TFA (each in a concentration of 1 mol/l) leads within a few minutes to the formation of considerable amounts of *(4)*, according to the ^{1}H-NMR spectrum[5].



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

Treatment of the reaction mixture after 30 min at 20 °C with an excess of thioglycolic acid *(5)*[6,7] affords up to 60% of *S*-(α-ferrocenylisobutyl)thioglycolic acid *(6)* while 35% of ferrocene *(1)* can be recovered. After 3 h, the yield of *(6)* increases to 80% and ferrocene can no longer be isolated.

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This reaction is of preparative importance because *(6)* can readily be converted into *(7)*; previous syntheses[3] were much more complicated.

Procedure

Synthesis of *(6)*: Compounds *(1)* (1.86 mmol) and *(2)* (1.8 ml, 20 mmol) are dissolved in TFA (10 ml) and stirred at room temperature for 3 h. Compound *(5)* is added (5 ml, 70 mmol), stirring continued for 15 min, and the mixture slowly neutralized with saturated $NaHCO_3$ solution until the greenish brown color turns to orange. The mixture is treated with 10% caustic soda (100 ml) and CH_2Cl_2 (100 ml). The phases are separated, the organic phase is extracted one more with 10% caustic soda (100 ml) and twice with water (2 × 100 ml) and the combined aqueous solutions are finally extracted twice with CH_2Cl_2. The aqueous phase is acidified with sulfuric acid until incipient precipitation of *(6)* gives rise to a yellowish white turbidity. After extracting three times with CH_2Cl_2, the combined extracts are dried with sodium sulfate, and the solvent removed under reduced pressure. Compound *(6)* is obtained as a red oil which slowly crystallizes. It is recrystallized from ether and cyclohexane; yield 2.65 g (80%), m.p. 82 °C.

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CAS Registry numbers:
(1), 102-54-5; *(2)*, 78-84-2; *(3)*, 51177-17-4; *(4)*, 67577-01-9; *(5)*, 68-11-1; *(6)*, 63393-49-7; *(7)*, 64598-90-9

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Hydrosulfuration-Thionation of Unsaturated Amides[**]

By *Howard Alper, Janie K. Currie*, and *Rajeev Sachdeva*[*]

In 1973, *Scheeren et al.*[1] reported that carbonyl compounds could be converted into the corresponding thiocarbonyls by the use of tetraphosphorus decasulfide and sodium bicarbonate in acetonitrile or ether solvents. We have found this method to be a very useful one for the synthesis of aromatic and aliphatic thioketones[2]. However, when we applied this procedure to unsaturated amides, an interesting reaction occurred to give a saturated thioamide.

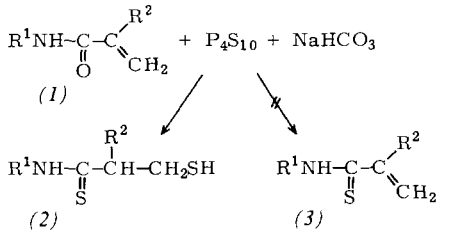
α,β-Unsaturated amides *(1)*, prepared by treatment of an aromatic amine with acryloyl or methacryloyl chloride, react with P_4S_{10} and $NaHCO_3$ in acetonitrile to give the β-mercaptoalkyl thioamides *(2)* in 31—56% yields (Table 1). None

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of the anticipated thioamide *(3)* was isolated from these reactions.

The proton (Table 1) and carbon magnetic resonance data are in accord with the assigned structure *(2)*. All of the compounds gave molecular ion peaks in the mass spectra,



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

Table 1. *N*-Aryl-β-mercaptoalkylthioamides *(2a)*—*(2e)* prepared.

	R^1	R^2	Yield [%]	m.p. [°C]	^{1}H-NMR, δ values [a]
a	*p*-$CH_3OC_6H_4$	H	45	91—93	1.75 (t, 1H, SH*), 2.84—3.08 (m, 4H, CH_2CH_2), 3.67 (s, 3H, OCH_3), 6.88 (d, 2H, *m*-H, *J* = 9 Hz), 7.52 (d, 2H, *o*-H), 8.50 (s, 1H, NH*)
b	*p*-$CH_3OC_6H_4$	CH_3	46	60—62	1.43 (d, 3H, CH_3), 1.67 (t, 1H, SH*), 2.68—3.17 (m, 3H, CH_2CH), 3.82 (s, 3H, OCH_3), 6.93 (d, 2H, *m*-H, *J* = 9 Hz), 7.58 (d, 2H, *o*-H)
c	2,6-$(CH_3)_2C_6H_3$	CH_3	31	125—126	1.47 (d, 3H, $CHCH_3$), 1.83 (t, 1H, SH*), 2.23 (s, 6H, *o*-CH_3), 2.95 (m, 2H, CH_2), 3.28 (*m*, 1H, $CHCH_3$), 7.23 (br. s, 3H, *m*-H, *p*-H)
d	*p*-$CH_3C_6H_4$	CH_3	42	89—90	1.42 (d, 3H, $CHCH_3$), 1.67 (t, 1H, SH*), 2.35 (s, 3H, *p*-CH_3), 2.93 (m, 2H, CH_2), 3.20 (m, 1H, $CHCH_3$), 7.32 (d, 2H, *m*-H, *J* = 8 Hz), 7.69 (d, 2H, *o*-H)
e	*p*-ClC_6H_4	CH_3	56	104—106	1.40 (d, 3H, CH_3), 1.63 (t, 1H, SH*), 2.55—3.20 (m, 3H, $CHCH_2$), 7.35 (d, 2H, *m*-H, *J* = 9 Hz), 7.72 (d, 2H, *o*-H)

[a] In $CDCl_3$; protons that are exchangeable with D_2O are marked with an asterisk. *o* = C^2 and C^6, *m* = C^3 and C^5, *p* = C^4 in phenyl substituents.

followed by loss of H_2S, and then fragmentation of the olefin to give the isothiocyanate radical ion.

The transformation of *(1)* to *(2)* may proceed *via* Michael addition of SH^- to the unsaturated amide, followed by conversion of the carbonyl into the thiocarbonyl function. Alternatively, compound *(3)* may be formed first, with subsequent Michael addition of SH^- to give *(2)*.

The reaction described above enables one to functionalize a thioamide with a thiol group, the latter serving as a useful entry to other functionalities, and to heterocycles, *via* appropriate reactions[3].

Procedure

Synthesis of *(2)*: To a stirred acetonitrile (80 ml) solution of the amide *(1)* (5—10 mmol) was added P_4S_{10} (1.5 equiv.) followed by $NaHCO_3$ (6.0 equiv.). The reaction mixture was stirred at 70°C for 1—2 h (or 30°C overnight), concentrated *in vacuo*, and ether was added to the residue. The ether solution was washed several times with water, dried ($MgSO_4$), and evaporated to give crude *(2)*. Pure *(2)* was obtained by silica gel chromatography using 5:1 benzene/ether as the eluant.

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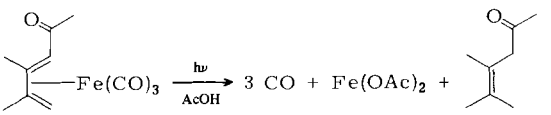
CAS Registry numbers:
(1a), 7766-37-2; *(1b)*, 7274-71-7; *(1c)*, 54054-63-6; *(1d)*, 2918-73-2; *(1e)*, 2918-77-6; *(2a)*, 67523-61-9; *(2b)*, 67523-62-0; *(2c)*, 67523-63-1; *(2d)*, 67523-64-2; *(2e)*, 67523-65-3; P_4S_{10}, 12066-62-5

[1] *J. W. Scheeren, P. H. J. Ooms, R. J. F. Nivard*, Synthesis *1973*, 149.
[2] *E.g., H. Alper, H. N. Paik*, J. Am. Chem. Soc. *100*, 508 (1978).
[3] *R. K. Olsen, J. O. Currie, Jr.* in *S. Patai*: The Chemistry of the Thiol Group, Part 2. J. Wiley, New York 1974, pp. 519—588.

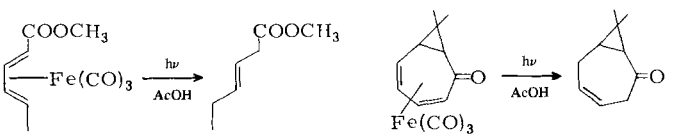
Regioselective Hydrogenation and Carbonylation of Functionalized Dienes on Photocleavage from Their Tricarbonyliron Complexes[**]

By *Michel Franck-Neumann, Daniel Martina*, and *Francis Brion*[*]

Dienes can usually be oxidatively cleaved from their tricarbonyliron complexes without undergoing any change in structure—however, in certain cases the formation of undesirable by-products takes place[1]. But a change in structure can be preparatively advantageous, if it proceeds in a defined manner. We have now found that tricarbonyliron complexes of 1,3-dienes which are substituted by electron-withdrawing groups in the 1-position are converted regiospecifically into β,γ-unsaturated compounds on photolysis in acetic acid. Thus, for example, the complexes of aliphatic dienones *(1)*, diene esters *(3)*, or cyclic dienones *(5)* are cleanly converted, respectively, into the β,γ-unsaturated carbonyl compounds *(2)*, *(4)*, and *(6)* which can be isolated in good yields.

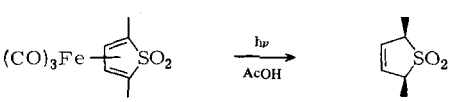


(1) *(2)*, 80%



(3) *(E)*-*(4)*, 98% *(5)* *(6)*, 90%

Also the complexed diene *(7)* containing a sulfonyl group is converted specifically into a dihydrothiophene. Only the *cis*-dimethyl isomer *(8)*[2] is formed. The two hydrogen atoms are therefore added from the same side.

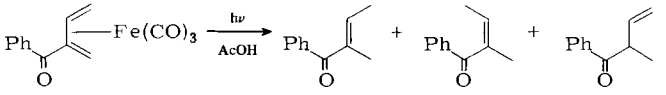


(7) *(8)*, 75%

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[**] This work was supported by the Centre National de la Recherche Scientifique (ATP n° 2238).

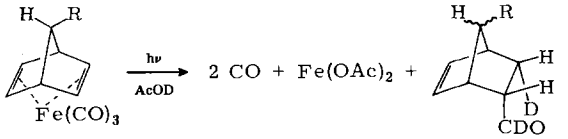
Diene complexes which are substituted in the 2-position, or do not bear electron-withdrawing substituents, react less specifically[3]. For example, the complex *(9)* yields a mixture of the isomeric enones *(10)*, *(11)*, and *(12)*, with the 1,4-addition of hydrogen strongly predominating.



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

5 : 4 : 1

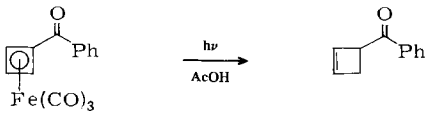
In the case of norbornadiene complexes these reductive photocleavages[4] can be accompanied by carbonylation. Thus, the complexes *(13)*, which do not contain any electron-withdrawing groups on the unsaturated system[5], are converted stereospecifically into *endo*-norbornenecarbaldehydes *(14)*[6], a reaction corresponding to a hydroformylation. Both addition processes thus proceed stereospecifically on the metal side.



(13a), R = H
(13b), R = O*t*Bu

(14a), R = H, 80%
(14b), R = O*t*Bu, 80% (2 isomers)

The preparative utility of these photocleavage reactions would seem to lie mainly in the synthesis of β,γ-unsaturated esters and ketones whose preparation *via* alternative routes presents difficulties. As example we might mention the cyclobutadiene complex *(15)*, which behaves as a 1-benzoyl-1,3-diene complex on photocleavage in acetic acid and gives exclusively 2-cyclobutenyl phenyl ketone *(16)*.



(15) *(16)*, 85%

Procedure

(15)[7] (594 mg, 2 mmol) is dissolved in 100 ml acetic acid. The solution, through which nitrogen is passed, is irradiated with a 125 W high-pressure mercury-vapor lamp until elimination of CO is complete (*ca.* 440 ml in 30 min). After addition of 150 ml water the solution is extracted four times with pentane (total volume 200 ml). The combined extracts are washed with water, 10% sodium hydrogen carbonate solution, once again with water, and then dried over magnesium sulfate. After removal of solvent the residual liquid is filtered over 10 g SiO_2; 263 mg (85%) analytically pure *(16)* is obtained as an almost colorless liquid; IR: ν(C=O): 1685 cm^{-1}, ν(C=C): 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.90 (2H, d, $J \approx 3.5$ Hz), 4.51 (1H, t, $J \approx 3.5$ Hz), 6.23 (2H, s), 7.40—8.05 (5H, m).

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CAS Registry numbers:
(1), 31833-14-4; *(2)*, 3744-02-3; *(3)*, 33593-81-6; *(4)*-(*E*), 13894-61-6; *(5)*, 57407-42-8; *(6)*, 67598-37-2; *(7)*, 37048-09-2; *(8)*, 10565-35-2; *(9)*, 12087-05-7; *(10)*, 20047-50-1; *(11)*, 20047-49-8; *(12)*, 50599-02-5; *(13a)*, 12307-07-2; *(13b)*, 67612-83-3; *(14a)*, 67598-38-3; *(14b)*, 67598-39-4; *(15)*, 67612-84-4; *(16)*, 67598-40-7

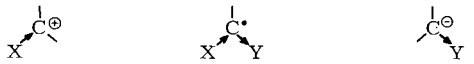
[1] *M. Franck-Neumann, D. Martina*, Tetrahedron Lett. *1975*, 1759; *1977*, 2293.
[2] *W. L. Mock*, J. Am. Chem. Soc. *88*, 2857 (1966).
[3] For example, reaction of tricarbonyliron complexes with 1,4-diphenylbutadiene or cyclooctatetraene yields mixtures of olefins.
[4] Monoene-Fe(CO)$_4$ complexes such as methyl acrylate-tetracarbonyliron are reduced to saturated compounds: *E. A. Koerner von Gustorf, F. W. Grevels, M. K. Das, O. Jaenicke, R. Knoesel*, Manuscript No. 36, 4th IUPAC Symposium on Photochemistry, Baden-Baden 1972. *F. W. Grevels* and *W. Schlamann* have also investigated simple diene complexes (private communication).
[5] Iron complexes of norbornadiene carboxylates are only converted into non-conjugated norbornene carboxylates.
[6] The Diels-Alder addition of acrolein to cyclopentadiene likewise affords the aldehyde *(14a)*, though in admixture with the *exo*-derivative.
[7] *J. D. Fitzpatrick, L. Watts, G. F. Emerson, R. Pettit*, J. Am. Chem. Soc. *87*, 3254 (1965).

Stabilization of Radicals by "Capto-Dative" Substitution – *C—C* Addition to Radicophilic Olefins

By *Lucien Stella, Zdenek Janousek, Robert Merényi*, and *Heinz Günter Viehe*[*][**]

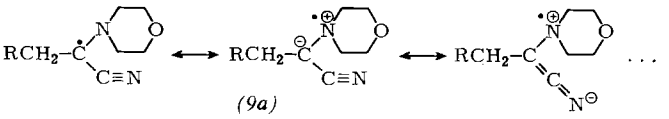
Dedicated to Professor Horst Böhme on the occasion of his 70th birthday

Whereas carbanions are stabilized by electron acceptors and carbocations by electron donors, radicals are stabilized by simultaneous substitution with a donor and an acceptor group ("capto-dative substitution"[1]).



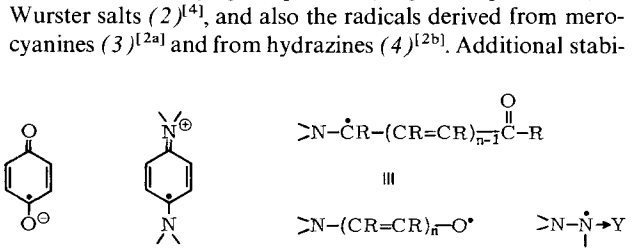
X = Donor, Y = Acceptor

Although this effect has already been discussed[2], it has hardly been utilized. It is evident from the resonance structures of the radical *(9a)*, and has been confirmed by *ab initio* calculations[3].



(9a)

Many of the known persistent radicals have capto-dative substituents in *vinylogous* positions, *e.g.* semiquinones *(1)*, Wurster salts *(2)*[4], and also the radicals derived from merocyanines *(3)*[2a] and from hydrazines *(4)*[2b]. Additional stabi-



(1) *(2)* *(3)* *(4)*

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[**] We thank *A. R. Katritzky, G. Smets, J. M. Tedder, J. C. Walton*, and *P. Gouverneur* for valuable discussions.

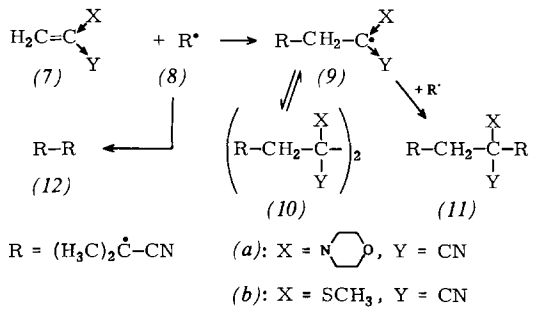
lization often comes from the presence of further aromatic substituents[5].

Our interest centers on radicals with *directly* capto-dative substituted carbon atoms, *i.e.* very simple systems without olefinic resonance or particular steric stabilization. Among such species only the radicals *(5)* and *(6)* are known[6].



(5) *(6)*

We have now found that 1,1-capto-dative substituted olefins *(7)*[7] do not polymerize with isobutyronitrile radicals *(8)*, but instead undergo addition to form radicals of type *(9)* which are stable in the hot reaction mixture and either dimerize to *(10)* on cooling or react with *(8)* to form the bis-adduct *(11)*.



R = $(H_3C)_2\dot{C}$–CN *(a)*: X = , Y = CN

(b): X = SCH_3, Y = CN

Table 1. Properties of the products *(10)* and *(11)*.

	M.p. [°C]	M_r	^{1}H-NMR: δ in $CDCl_3$
(11a)	152	274	1.55, 1.63, and 1.65 (3H, 3H, and 6H, s), 1.94 and 2.61 (2H, AB system, J = 15.2 Hz), 3.21 (4H, m), 3.8 (4H, m)
(11b)	96	235	1.57, 1.60, 1.62, and 1.64 (each 3H, s), 1.95 and 2.24 (2H, AB system, J = 15 Hz), 2.55 (3H, s)
(10b)	152—153	334	1.59 and 1.65 (each 6H, s), 2.43 and 2.45 (4H, AB system, J = 15 Hz), 2.73 (6H, s)
(10b')	166—167	334	1.58 and 1.64 (each 6H, s), 2.11 and 2.33 (4H, AB system, J = 15 Hz), 2.68 (6H, s)

Thus, under the conditions given in the *Procedure*, *(7a)* furnishes only *(11a)* in 70% yield, whereas *(7b)* affords 18% of *(11b)* together with 51% of the monoadduct dimer *(10b)* as a mixture of the *meso* and DL form. The radicophilic nature of the olefins *(7)* is so pronounced that they act as polymerization inhibitors[8].

The ESR spectra recorded in the hot [mixture of olefin and azoisobutyronitrile, *(9a)*: 90°C, *(9b)*: 120°C, in chlorobenzene, or for *(9b)* from the dimers *(10b)* and *(10b')* at the same temperature] are in accord with the proposed structures (Table 2).

Table 2. The g values and hyperfine coupling constants determined by ESR spectroscopy for radicals *(9)*.

	g	a_N [G]		a_H [G]	
		—CN	—NR_2	—CH_2— (chain)	—NCH_2— (ring) —SCH_3
(9a)	2.0032	2.94	7.9	10.12	7.12
(9b)	2.0056	2.75	—	9.14	3.68

On heating to 100°C in chlorobenzene solution, the racemate *(10b')*[9] gives a 4:1 equilibrium mixture with the *meso* form *(10b)*.

Procedure

2-Azoisobutyronitrile (50 mmol) and olefin *(7)* (100 mmol) are dissolved in dry benzene (80 ml) in a 120-ml ampoule, which is then degassed in three freeze-thaw cycles and sealed under vacuum. It is subsequently heated to 75—80°C in an oil-bath for 15 h. The solvent is evaporated off and the dimer *(12)* extracted with light petroleum (b.p. 60 to 90°C). The bis-adduct *(11)* can then be extracted with diethyl ether. The insoluble residue in the case of *(7b)* consists of the *meso* form *(10b)* and the DL form *(10b')* of the dimer of *(9)*. After recrystallization from benzene/cyclohexane (4:1), large crystals of *(10b')* can be gleaned from the powder-like precipitate of *(10b)*.

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CAS Registry numbers:
(7a), 5807-03-4; *(7b)*, 10568-85-1; *(8)*, 3225-31-8; *(9a)*, 67598-67-8; *(9b)*, 67598-68-9; *(10b)*, 67598-69-0; *(10b)*, 67598-70-3; *(11a)*, 67598-71-4; *(11b)*, 67598-72-5; *(12)*, 3333-52-6

[1] We prefer this designation over the terms "*mero*-stabilization" [2a] or "push-pull substitution" [2b].

[2] a) *R. W. Baldock, P. Hudson, A. R. Katritzky, F. Sati*, J. Chem. Soc. Perkin Trans. I *1974*, 1422; b) *A. T. Balaban*, Rev. Roum. Chim. *16*, 725 (1971); *A. T. Balaban et al.*, Tetrahedron *33*, 2249 (1977).

[3] LCAO/SCF: *G. Leroy, D. Peeters, L. Stella, Z. Janousek, R. Merényi, H. G. Viehe*, to be published.

[4] Review: *K. Deuchert, S. Hünig*, Angew. Chem. and Angew. Chem. Int. Ed. Engl., in press.

[5] *K. D. Gundermann, E. Röhrl*, Justus Liebigs Ann. Chem. *1974*, 1661; *H. G. Aurich, B. Deutschle, W. Weiss*, J. Chem. Res. (S) *1977*, 301.

[6] *L. de Vries*, J. Am. Chem. Soc. *99*, 1982 (1977); *100*, 926 (1978); *N. Heimer*, J. Org. Chem. *42*, 3767 (1977).

[7] *(7a)*: *S. C. Temin*, J. Org. Chem. *22*, 1714 (1957); *(7b)*: *K. D. Gundermann, R. Thomas*, Chem. Ber. *89*, 1263 (1956).

[8] *W. Naarmann, W. Wittmer*, BASF AG, personal communication.

[9] X-Ray structure analysis: *M. Van Meerssche, G. Germain, J. P. Declercq.*

Hexakis(2,6-di-*tert*-butyl-4-biphenylyl)ethane—The First Unbridged Hexaarylethane[**]

By *Martin Stein, Werner Winter*, and *Anton Rieker*[*]

Ever since *Gomberg*'s first attempt to synthesize hexaphenylethane *(1a)* some 80 years ago under the guidance of *V. Meyer* in Heidelberg, this molecule has fascinated generations of chemists[1], and has still remained elusive. The dimer of triphenylmethyl *(2a)*, for decades regarded as *(1a)*, was shown as late as 1968 to be the methylenecyclohexadiene derivative *(3a)* (Jacobson-Nauta structure)[2,3].

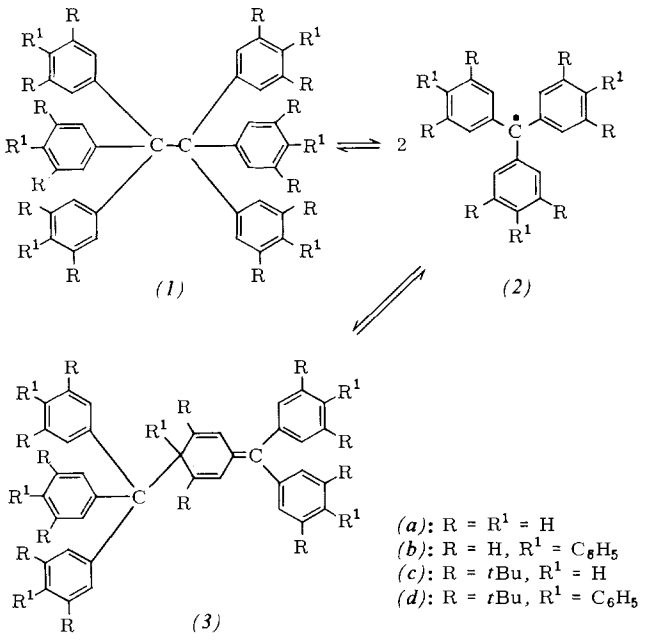
The reason for the dimerization of triphenylmethyl to *(3a)* probably lies in the steric hindrance between the hydrogen atoms *ortho* to the benzyl C-atom in structure *(1)*. When two, four, or all six *ortho* positions in *(2)* are bridged directly

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[+] Dr. *Winter* carried out the X-ray structure analyses.

[++] Author to whom correspondence should be addressed.

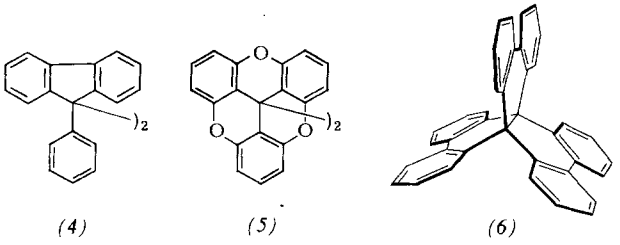
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



(1) (2) (3)

(a): R = R¹ = H
(b): R = H, R¹ = C₆H₅
(c): R = tBu, R¹ = H
(d): R = tBu, R¹ = C₆H₅

or *via* intermediate units the hexaarylethanes are stable, *e.g.* *(4)*[3a], *(5)*[4], or *(6)*[5] (for further examples cf.[6]).



(4) (5) (6)

According to calculations by *Mislow et al.*[6], hexaphenylethane *(1a)* ought to be capable of existing with a central CC bond length of 164 pm and suitably intermeshed phenyl rings (point group D_3). Two routes would appear particularly promising for the synthesis of *(1a)* or a derivative thereof: 1) Synthesis of one or more phenyl rings in a molecule already containing the central CC bond. 2) Steric hindering of formation of the Jacobson-Nauta structure by incorporation of bulky groups R^1 and/or R; *(2)* must then either be persistent as the monomer—or dimerize (kinetically controlled) to *(1)*, which should be isolable if the dissociation equilibrium is established slowly.

In connection with our studies on the structure of twisted π-electron systems[7a] and on the reason for the monomeric character of the Schlenk radical *(2b)*[7b], we chose the second route.

According to *Berndt et al.*[8] the initially synthesized radical *(2c)*[7a,8] is monomeric in the solid state. However, on evaporating a solution of *(2c)* in cyclohexane colorless crystals of a dimer are obtained which on redissolution afford a yellow solution of *(2c)* (ESR spectrum). The concentration of radicals in a solution of *(2c)* obtained on warming the dimer in benzene decreases to a constant value over the course of 6 days (degree of dissociation *ca.* 55 % for an initial concentration of dimer of 8.13×10^{-3} mol/l). Evaporation of this solution affords red crystals which still contain benzene and *(2c)*.

Because of the high degree of dissociation and the sensitivity of the radical towards traces of oxygen no definite proof of the structure of *(1c)* can be obtained with ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy, though the length of time required for equilibration would indicate the ethane structure[2].

The radical *(2d)*[7a,9] also dimerizes. The dimer is much more sparingly soluble than dimeric *(2c)* and it dissociates much more slowly to the radical; for a 1.6×10^{-3} M solution of the dimer in benzene the equilibrium degree of dissociation is *ca.* 63 %. The mass spectrum (field desorption technique) shows only the signal of the radical *(2d)*; the IR spectrum (KBr), on comparison with that of the corresponding triarylmethanol, the triarylmethyl chloride, and the triarylmethyl peroxide, indicates the ethane structure *(1d)*. Because of the sparing solubility of the dimer in all common solvents, ^{1}H- and ^{13}C-NMR spectroscopy were here also of little help in deciding between the structures *(1d)* and *(3d)*. On the other hand, the dimer of the radical *(2d)* enriched with 90 atom-% ^{13}C in the benzyl position ($a_{^{13}C} = 2.31$ mT), shows, in hexadeuteriobenzene, in addition to the three signals of the solvent only *one* further signal at $\delta = 70.7$ (the shift value appears plausible for the benzyl carbon of a trityl group[3a]). In order to keep the content of monomeric radical *(2d)* in the solution as low as possible the dimer was brought into solution without warming. The ^{13}C-NMR spectrum is consistent only with structure *(1d)*; for *(3d)* two signals at $\delta = 62$—65 and 135—140 would be expected[3a].

The dimer of the radical *(2d)* could be obtained as colorless crystals (m.p. 276 °C) suitable for X-ray structural analysis after seven months of isothermal concentration of a benzene solution in absence of air. Structural analysis[10] showed that this species is in fact a hexaphenylethane derivative *(1d)*.

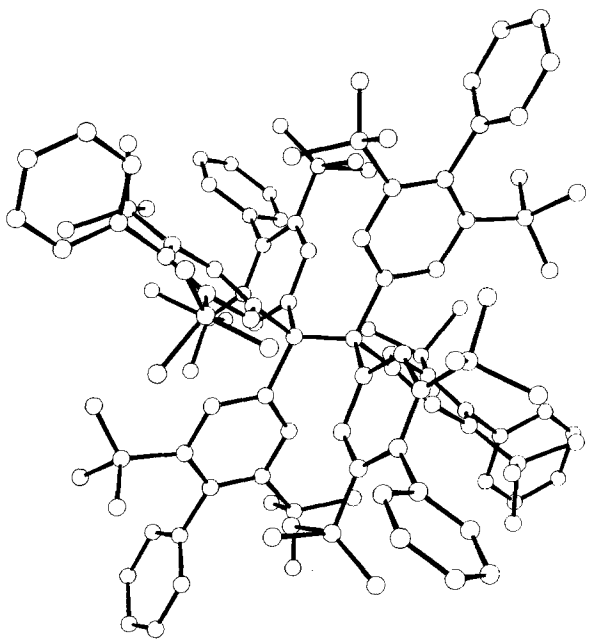


Fig. 1. Molecular structure of *(1d)* in the crystal.

In *(1d)* the heterochiral trityl propellers are staggered (point group S_6). This finding is contradictory to the force field calculations recently carried out by *Mislow et al.*[6], according to which the ground state of the D_3 conformation with homochiral trityl propellers in *(1a)* ought to be *ca.* 10.7 kJ/mol more stable than the ground state of the S_6 conformation. The central CC bond lengths [147(2) pm] and the C_{ethane}—C_{phenyl} bond lengths [average 165(3) pm] likewise differ markedly from the values calculated for *(1a)* (163.6 and 157.6 pm)[6]. Presumably, the *tert*-butyl groups are responsible for this effect.

The high melting point and slow dissociation of *(1d)* in solvents such as petroleum ether or benzene at room tempera-

ture would suggest that the unsubstituted hexaphenylethane *(1a)* should also by synthesizable.

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CAS Registry numbers:
(1a), 17854-07-8; *(1c)*, 67598-44-1; *(1d)*, 67598-45-2; *(2c)*, 50673-36-4; *(2d)*, 57244-80-1

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[10] Monoclinic, $P2_1/c$; $a=1385$, $b=1586$, $c=2670$ pm, $\beta=114.95°$; $Z=2$. Intensity measurement: Nonius-CAD 4; the crystals employed contained 4 molecules of solvent benzene per unit cell and effloresced at room temperature; the measurements were therefore carried out at $-130°C$. The phase determination could only be accomplished using "negative quartets" (we thank Dr. *E. Hädicke*, Ludwigshafen, for use of his version of the XCSD-SHELX program by *G. M. Sheldrick*, Cambridge). Refinement: $R=0.13$ for 1480 reflections with $I>2.7\sigma(I)$, isotropic temperature factors, benzene rings as rigid groups. Due to the poor quality of the crystals, the bond lengths quoted in the text are to be regarded as preliminary values.

β-Cyclodextrin Dodecahydrate: Crowding of Water Molecules within a Hydrophobic Cavity

By *Klaus Lindner* and *Wolfram Saenger*[*]

The inclusion of guest molecules in the cyclodextrin cavity[1] has been the object of thermodynamic[2, 3], kinetic[2], theoretical[4], and X-ray structural[5a] studies, especially with α-CD and β-CD, the cyclohexa- and heptaamyloses. Hydrophobic, van der Waals and dipole interactions, and release of conformational strain and hydrogen bonding[5b] energy have all been discussed as driving forces of complex formation. The latter were proposed on the basis of a comparative X-ray crystal study of the "empty" α-CD hexahydrate and α-CD guest complexes[5]. In order to examine the mechanistic conclusions for the larger β-CD, we have now performed an X-ray structural investigation on its hydrate form.

β-CD crystallizes from water as chunky prisms, space group monoclinic $P2_1$ and cell constants $a=21.29$, $b=10.33$, $c=15.10$ Å, $\beta=112.4°$. Cell volume and crystal density (1.453 g/cm³) indicate that the asymmetric unit consists of β-CD· dodecahydrate. The crystal structure was solved with the aid of an isomorphous derivative[6] β-CD·2HI·8H_2O. Present refinement has reached $R=8.3$ % for 6426 X-ray data for the HI complex and $R=7.1$ % for 5036 data for the dodecahydrate.

In both the dodecahydrate and in the 2HI·8H_2O complex, β-CD adopts an almost "round" shape, similar to that in the complexes with other guests[7]. All glucoses are in the C1 chair conformation and arranged such that a ring of hydrogen bonds O(2)···O(3) is formed between adjacent glucoses. The only significant differences between the various β-CD complexes are in the orientations of the C(6)—O(6) bonds which are generally turned "away" from the center of β-CD with torsion angles O(5)—C(5)—C(6)—O(6) corresponding to (−)*gauche*. In the 12H_2O complex, three C(6)—O(6) bonds are rotated "inwards" [(+)*gauche*] to participate in hydrogen bonding with included water molecules (cf. Fig. 1).

Compared with α-CD, the van der Waals cavity diameter is increased from 5.0 Å in α-CD to 6.7 Å in β-CD. The O(4) atoms lie on a circle of radius 4.3 Å in α-CD but 5.1 Å in β-CD and the angles at O(4) are decreased by 2°, relative to α-CD. The change of ring size is accompanied by a slight conformational change of the glucoses, C(4) deviating by 0.70 Å from the C(2), C(3), C(5), O(5) glucose plane in β-CD, but 0.63 Å in α-CD[5a].

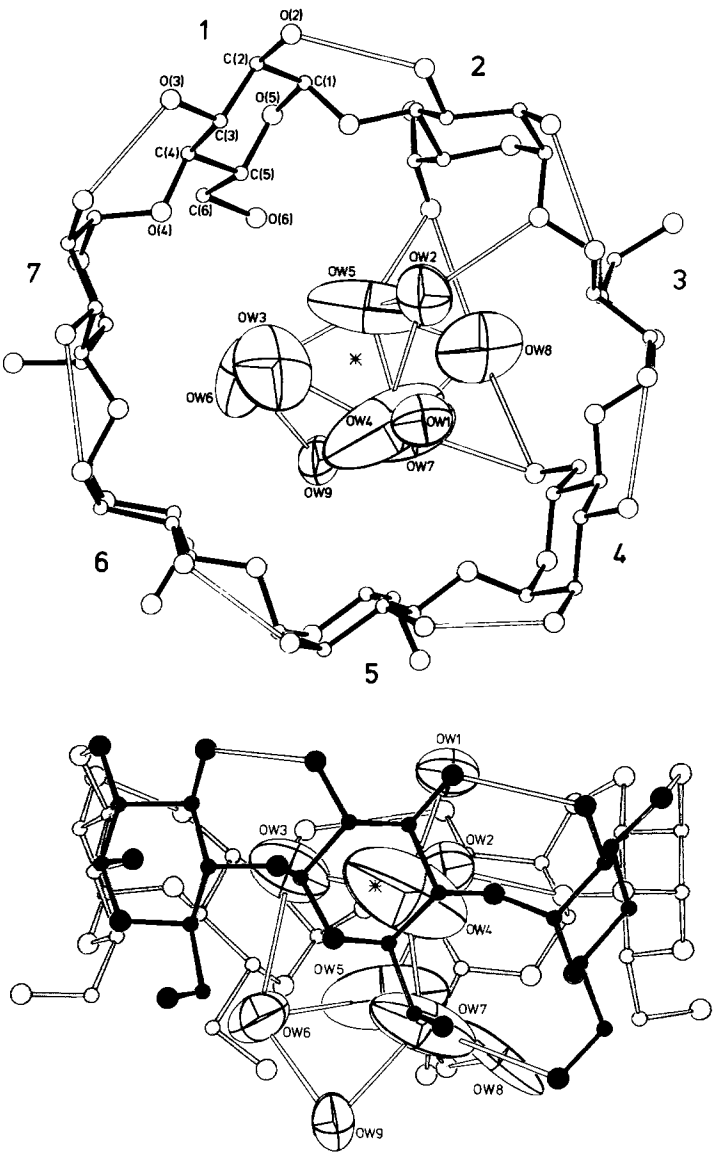


Fig. 1. Above: structure of β-cyclodextrin dodecahydrate from the O(2), O(3) side, water molecules within the cavity are drawn with their 50 % probability ellipsoids, water outside the cavity is omitted except OW9. Hydrogen bonding distances are indicated by open lines. The center of the ring formed by the seven O(4) atoms is marked by an asterik. Occupancies for water are 100 % for OW1, OW3; 89 % for OW4; 85 % for OW6; 73 % for OW5; 68 % for OW7, OW8; 61 % for OW2. The atom numbering scheme for glucose unit 1 is shown. In the text, *e.g.* O(3)2 refers to atom O(3) of glucose 2. O(6)2 is twofold disordered.

Below: The β-CD molecule viewed from the side, glucose unit 5 in front. Parts of the β-CD ring closer to the viewer are shaded more heavily than parts in the back. OW9 is already "outside" the cavity.

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The β-CD cavity is filled by 6.5 water molecules distributed statistically over eight sites (Fig. 1). The remaining 5.5 water molecules of the dodecahydrate are spread over eight sites between β-CD molecules. Because no water hydrogen atoms could be located, the assignment of hydrogen bonds must be based on distance criteria. One of the O···O distances, (OW5···OW8, 2.32 Å) indicates that both sites cannot be occupied simultaneously. All other O···O contacts between oxygen atoms within the cavity (2.6 Å to 3.0 Å) satisfy the generally accepted distance criteria, The OW2···O(4)3 distance of 2.98 Å may possibly indicate the first observed hydrogen bond to glycosidic oxygen in saccharide crystal structures. All other OW···O(4) contacts exceed 3.3 Å.

The water molecules near O(2), O(3), and near the O(6) rims are also in contact with hydroxyl groups of adjacent β-CD molecules, establishing a hydrophilic surface of the β-CD• water complex. The usual tetrahedral arrangement of hydrogen bonding donor and acceptor groups around water molecules is only verified for OW1, with O···OW1···O angles in the range 91° to 141° deviating significantly from the ideal 107°. Tetrahedra around OW2 and OW4 are even more distorted and OW3 has only three neighbors at suitable distances. The remaining four water sites within the cavity have five neighbors each, with O···OW···O angles from 50° to 166°.

In the "empty" α-CD•6 H_2O, two water molecules are located within the cavity[5b,8]. They are at fixed, fully occupied positions and hydrogen bonded with each other and with two O(6) hydroxyl groups. The α-CD ring is strongly deformed by rotation of one glucose unit into a nearly vertical position relative to the other five, and the ring of O(2)···O(3) hydrogen bonds is disrupted. In all other complexes, the α-CD molecule is "round" and the ring of O(2)···O(3) hydrogen bonds is fully established. This conformational change between "empty" and "full" α-CD has led to the proposal of an "induced fit"-like mechanism[5b].

The larger β-CD molecule exists in β-CD•12 H_2O in a "round" structure and no conformational change except rotation of C(6)—O(6) bonds is observed upon complex formation with other guests. Thus an "induced fit" type mechanism can be ruled out for β-CD.

Hence we infer that the driving force of complex formation is provided mainly by hydrophobic forces and by van der Waals interactions between guest molecules and the interior of the β-CD cavity. "Activated water" may also come into play because the coordination of the water molecules entrapped within the β-CD cavity is by no means "ideal" and some hydrogen bonding energy might be gained by expulsion of these water molecules. Further, entropy terms will be appreciable if the eight water molecules are expelled.

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CAS Registry number:
β-Cyclodextrin dodecahydrate, 20986-19-0

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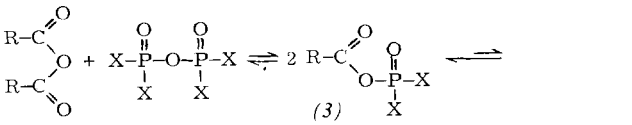
Mixed Carboxylic-Dichlorophosphoric Anhydrides—Reactive Intermediates in Acyl Chloride Synthesis with $POCl_3$[**]

By *Franz Effenberger, Gerd König*, and *Herbert Klenk*[*]

The intermediacy of mixed anhydrides *(3)*, X = Cl, has been proposed[1] in the preparation of acyl chlorides from salts of carboxylic acids and phosphoryl chloride. Acyl dichlorophosphates have likewise been advanced as the actual acylating agents in the "phosphoryl chloride method" developed by *Th. Wieland et al.* for the acylation of amino acids[2]. That no such intermediates *(3)* have yet been isolated or directly identified, is probably due to instantaneous reaction of the mixed anhydrides with nucleophiles still present in the mixture (carboxylate) or being formed in the course of the reaction (chloride).

We have now succeeded in preparing compounds *(3)* by reaction of carboxylic anhydrides *(1)* with dichloro- *(2a)* or difluorophosphoric anhydride *(2b)*. They are characterized by definite boiling points and correct elemental analyses; their structure is confirmed by ^{31}P- and ^{13}C-NMR spectra [*e.g. (3a)*: ^{31}P- (85 % H_3PO_4, ext.) $\delta = +1.66$; ^{13}C-NMR ($CDCl_3$) benzoyl carbon $\delta = 158.3$, $^2J_{O=C\ -O-P} = -11.5$ Hz].

In the case of anhydrides containing aliphatic acyl moieties, *e.g. (3e)* and *(3f)*, secondary processes such as ketene formation or condensation reactions prevent product isolation; however, these compounds can be prepared in dichloromethane solution. The NMR spectra provide unequivocal proof of both the presence and the structure of compounds *(3)*.



(1) *(2a)*, X = Cl; *(2b)*, X = F *(3)* 2 $[R-C\equiv O^{\oplus}\ PO_2X_2^{\ominus}]$ *(4)*

	R	X	Yield [%]	B.p. [°C/torr]
(3a)	C_6H_5	Cl	61	$77/10^{-3}$
(3b)	C_6H_5	F	80	$52/10^{-2}$
(3c)	p-$CH_3C_6H_4$	Cl	60	$97/10^{-3}$
(3d)	p-$CH_3C_6H_4$	F	75	$54/10^{-3}$
(3e)	CH_3	Cl	≈60 [a]	—
(3f)	CH_3	F	≈90 [a]	—

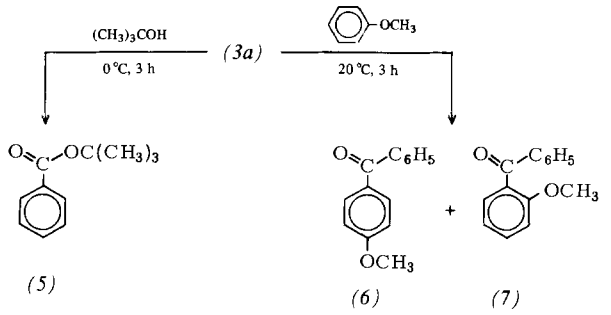
[a] Determined spectroscopically in CH_2Cl_2 solution.

Neither ^{31}P- nor ^{13}C-NMR shows any evidence of dissociation of the anhydrides *(3)* into acylium ions *(4)* which might be expected from the high leaving tendency of the dihalophosphate anion[3]. The IR spectrum also displays only a C=O vibration at 1780 cm^{-1} and no band at higher frequencies that could be attributed to stretching of the acylium function.

As expected, the anhydrides *(3)* are highly reactive. Unlike the corresponding acyl chlorides, they form esters of tertiary alcohols under mild conditions [*e.g. (5)*, 68 %]; with arenes, aryl ketones are produced *without* any Friedel-Crafts catalyst [*e.g. (6)* and *(7)*, 73 % (93:7)].

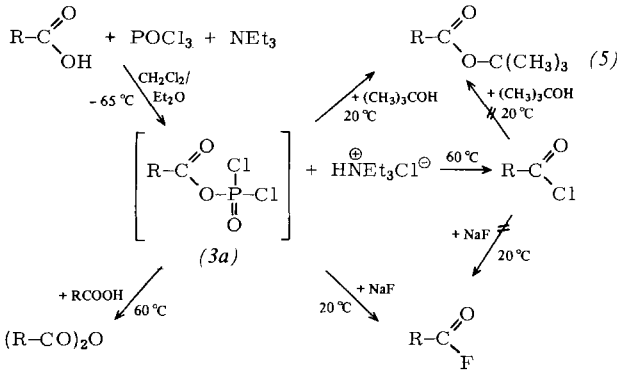
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As we were able to establish by ^{31}P-NMR and by chemical reactions, the formation of acyl chlorides from carboxylic acids and $POCl_3$ proceeds *via* acyl dichlorophosphates *(3)*. When benzoic acid, triethylamine, and $POCl_3$ are reacted in dichloromethane/ether at $-65\,^{\circ}C$, triethylammonium hydrochloride is precipitated. The presence of *(3a)* in the filtrate is demonstrated by the ^{31}P-NMR spectrum which remains unchanged upon admixture of authentic *(3a)*.

If the solution is warmed to 60 °C, benzoyl chloride and benzoic anhydride are formed; addition of alkali chlorides increases the percentage of acyl chloride. Apart from these two compounds, *tert*-butyl benzoate *(5)* is formed in the presence of *tert*-butanol at room temperature; benzoyl fluoride is produced upon addition of sodium fluoride and catalytic amounts of crown ether. Under these conditions, neither benzoyl chloride nor benzoic anhydride react with *tert*-butanol or NaF. Leaving group in each case is the dichlorophosphate ion, $Cl_2P(O)O^{\ominus}$.



R = C_6H_5

The above evidence definitely establishes the acyl dichlorophosphates *(3)* as true intermediates in the acyl chloride synthesis with $POCl_3$; at the same time, the high acylating potential of the mixed anhydrides *(3)* is demonstrated.

Procedure

Synthesis of *(3a)*: *(2a)*[4] (9.80 g, 38.8 mmol) and benzoic anhydride *(1)*, R = C_6H_5, (8.78 g, 38.8 mmol), are heated to 95 °C for 8 h, with strict exclusion of moisture. Fractional distillation of the reaction mixture yields 1.7 g (17%) of *(2a)*, b. p. 30 °C/10^{-3} torr, and 11.3 g (61%) of *(3a)*, b. p. 77 °C/10^{-3} torr.

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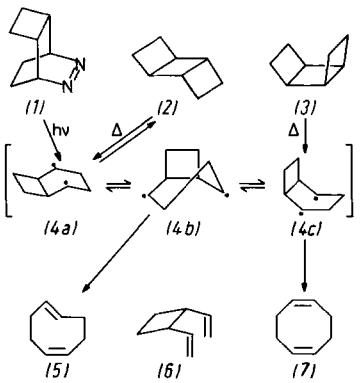
CAS Registry numbers:
(1) (R = C_6H_5), 93-97-0; *(2a)*, 13498-14-1; *(2b)*, 14456-60-1; *(3a)*, 67598-46-3; *(3b)*, 67598-47-4; *(3c)*, 67598-48-5; *(3d)*, 67598-49-6; *(3e)*, 67598-50-9; *(3f)*, 67598-51-0; *(5)*, 774-65-2; *(6)*, 611-94-9; *(7)*, 2553-04-0; *tert*-butyl alcohol, 75-65-0

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Novel Mode of Formation of *cis,trans*-1,5-Cyclooctadiene[**]

By *Hans-Dieter Martin, Bernd Heiser*, and *Michael Kunze*[*]

Highly strained, *trans*-configurated double bonds in eight-membered rings are usually generated by elimination[1a], olefin inversion[1b], electrocyclic ring-opening[1c], cycloreversion[1d], or thermolysis[1e]. Previously, the *cis,trans*-isomerization of *cis*-configurated double bonds has been used as photochemical method[2]. We report here on photochemical and thermal fragmentations of the cyclic azo compound *(1)*[3], which lead in partly satisfactory yields to *cis,trans*-1,5-cyclooctadiene *(5)*.



A detailed study of *(1)* was promoted by the previous finding that *(5)* is a major product of the thermally induced valence isomerization of the tricyclooctanes *(2)* and *(3)*[1e]; a diradicaloid *(4)* was postulated as product-determining intermediate having three possible conformations *(4a)*—*(4c)* fulfilling all the necessary geometrical requisites for stereoelectronically favorable cleavage. A consequence of this hypothesis was the search for further suitable precursors for *(4)* and thus also for *(5)*. From the preparative standpoint the fragmentation of 7,8-diazatricyclo[4.2.2.$0^{2,5}$]dec-7-ene *(1)* appeared the most suitable approach[3].

As expected, irradiation of *(1)* (λ_{max} = 384 nm, ε = 164) in pentane does in fact afford *(5)* as main product. In ether[3] the yield of *(5)* is considerably lower (see Table 1).

On separation of the products slight losses are incurred on account of the high sensitivity of *(5)*. Compound *(5)* was converted directly in the photolyzate with hexachlorocyclopentadiene.

Thermolysis of the tricyclic compound *(2)* under conditions (A) likewise leads to *(5)* as a major product. Under conditions

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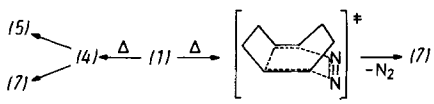
[**] Part 28 of the series "Small Rings". This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and BASF AG.—Part 27: *H.-D. Martin, R. Iden, H. J. Schiwek*, Tetrahedron Lett. *1978*, 3337.

Table 1. Photolysis and gas-phase thermolysis (flow system) of *(1)*, *(2)*, and *(5)*. Conditions (A): thermolysis at 300 °C/14 torr; conditions (B): thermolysis at 290 °C/34 torr.

Educt	Conditions	Product mixture [%] [a]			
		(2)	*(5)*	*(6)*	*(7)*
(1)	*hν*, pentane	22	53	12	13
(1)	*hν*, acetonitrile	19	59	11	11
(1)	*hν*, ether	45	18	19	18
(1)	*hν*, acetone	17	56	14	11
(2)	(A), 37 % conversion	63	17	4	15
(2)	(B), 91 % conversion	9	20	4	63
(5)	(B), 58 % conversion		42	5	50
(1)	(B), 40 % conversion	3	5	2	88

[a] In some cases the product mixture contains small amounts of *trans*-1,2-divinylcyclobutane and 4-vinylcyclohexene. The composition of the product mixture was determined gas-chromatographically directly after the photolysis or thermolysis.

(B) the thermolability of *(5)* and the isomerization to *(7)* become strikingly manifest. Also the thermolysis of *(5)* itself (conditions B) yields predominantly *(7)*. The thermolysis of *(1)* is worth noting. The formation of considerable amounts of *(5)* expected *a priori* is not observed; the main product is the *cis,cis*-diene *(7)*. This indicates that the thermal fragmentation of *(1)* *via* the diradicaloid *(4)* to the *cis,trans*-diene *(5)*—in contrast to the photochemical decomposition—takes place only to a minor extent, and that the concerted $[\sigma_s+\sigma_s+\sigma_s]$ fragmentation to *(7)* is the dominant reaction. This is in agreement with experiments[5] which demonstrate the ability of the cyclobutane ring to participate in the process,



and also reconcilable with the positive activation entropy of this process[6]. The supposition that *(1)* lies on the borderline between concerted and diradical decomposition[5] is thus confirmed.

Procedure

A solution of *(1)* (1.00 g, 7.35 mmol) in anhydrous and olefin-free pentane (40 ml) is irradiated (150 W Hg high-pressure lamp, Duran) for 6 h at −10 °C. The conversion of *(1)* amounts to 50 % (decrease in extinction of the $n_-\pi^*$ transition at 384 nm). After addition of 500 mg (1.85 mmol) hexachlorocyclopentadiene, the volatile components are removed in a water-pump vacuum and the residue is distilled at 135—145 °C/0.001 torr in a bulb-to-bulb apparatus; yield of adduct $C_{13}H_{12}Cl_6$[4] 360 mg (52 %); ^{1}H-NMR (60 MHz, CCl_4): $\delta = 1.80$—2.45 (m, 8H, CH_2), 2.50—2.75 (m, 1H, CH), 2.75—2.90 (m, 1H, CH), 5.65 (m, 2H, olefinic).

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CAS Registry numbers:
(1), 249-88-7; *(2)*, 13027-75-3; *(3)*, 28636-10-4; *(5)*, 5259-71-2; *(6)*, 16177-46-1; *(7)*, 1552-12-1; *trans*-1,2-divinylcyclobutane, 6553-48-6; 4-vinylcyclohexene, 100-40-3; adduct $C_{13}H_{12}Cl_6$, 67598-66-7

[1] a) See *e.g. J. L. Coke, M. C. Mourning*, J. Am. Chem. Soc. *90*, 5561 (1968); b) see *e.g. A. J. Bridges, G. H. Whitham*, J. Chem. Soc. Chem. Commun. *1974*, 142; c) *C. B. Reese, A. Shaw*, J. Chem. Soc. Perkin Trans. 1 *1975*, 2422; d) *M. Jones, P. Temple, E. J. Thomas, G. H. Whitham, ibid. 1974*, 433; e) *H.-D. Martin, E. Eisenmann*, Tetrahedron Lett. *1975*, 661; *H.-D. Martin, M. Hekman, G. Rist, H. Sauter, D. Bellus*, Angew. Chem. *89*, 420 (1977); Angew. Chem. Int. Ed. Engl. *16*, 406 (1977).
[2] See *e.g. J. A. Deyrup, M. Betkouski*, J. Org. Chem. *37*, 3561 (1972).
[3] *H. Tanida, S. Teratake, Y. Hata, M. Watanabe*, Tetrahedron Lett. *1969*, 5341; *E. L. Allred, J. C. Hinshaw, ibid. 1972*, 387.
[4] *K. Ziegler, H. Sauer, L. Bruns, H. Froitzheim-Kühlhorn, J. Schneider*, Justus Liebigs Ann. Chem. *589*, 122 (1954).
[5] *J. A. Berson, S. S. Olin, E. W. Petrillo, P. Bickart*, Tetrahedron *30*, 1639 (1974).
[6] *J. P. Snyder, D. N. Harpp*, J. Am. Chem. Soc. *98*, 7821 (1976).

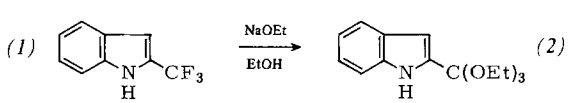
ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

Asymmetric syntheses are surveyed by *D. Valentine, Jr.*, and *J. W. Scott* with regard to preparative utility. Only those syntheses are considered in which the chiral molecules are generated exclusively by chemical reagents and the enantiomeric ratio is at least 3 : 1. Enamines and *N*-substituted imines, olefins without heteroatoms at the double bond, and carbonyl compounds serve as starting materials. [Asymmetric Synthesis. Synthesis *1978*, 329—356; 333 references]

[Rd 33 IE]

Reactions of CF_3-substituted arenes with nucleophilic reagents have been compiled by *Y. Kobayashi* and *I. Kumadaki*. The CF_3 group attached to aromatic compounds was formerly regarded as a very stable substituent, but it has meanwhile been found that CF_3 moieties present on quinolines, indoles, benzofurans, and benzene derivatives can undergo numerous reactions with nucleophiles. For instance, 2-(trifluoromethyl)-



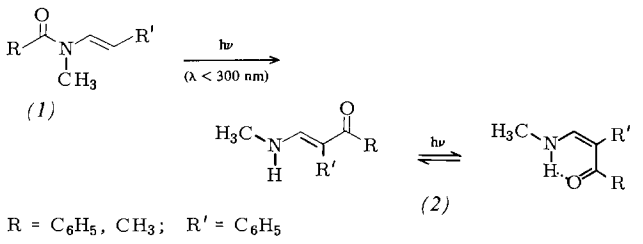
indole *(1)* gives the product *(2)* in an S_N1 reaction with $NaOC_2H_5$ in ethanol. Although benzotrifluoride is not attacked under these conditions, it can be degraded to *p*-aminobenzonitrile by $NaNH_2$ in ammonia after introduction of a *p*-amino group. [Reactions of Aromatic Trifluoromethyl Compounds with Nucleophilic Reagents. Acc. Chem. Res. *11*, 197—204 (1978); 20 references]

[Rd 31 IE]

The insoluble acid salts of tetravalent metals are surveyed by *G. Alberti*. Inorganic ion exchangers of this kind are of potential interest on account of their pronounced resistance to high temperatures and to radiation. The prototype $Zr(HPO_4)_2 \cdot H_2O$ crystallizes in a layer structure (interlayer distance 7.56 Å). The structure contains cavities interconnected by openings of maximum diameter 2.64 Å. In contrast to the zeolites the interlayer distance can be increased, *e.g.* by replacing a proton by sodium; in the resulting product $ZrHPO_4 \cdot NaPO_4 \cdot 5H_2O$ it is 7.6 to 11.8 Å. If Na^+ is now replaced by H^+, a new form arises containing $5—7 H_2O$ and having an interlayer distance of 10.4 Å in which the windows between the cavities are also enlarged, permitting exchange of large cations. [Syntheses, Crystalline Structure, and Ion-Exchange Properties of Insoluble Acid Salts of Tetravalent Metals and Their Salt Forms. Acc. Chem. Res. *11*, 163—170 (1978); 80 references]

[Rd 30 IE]

The photochemistry of enamides is examined by *G. R. Lenz*. Although rather unreactive in the ground state, enamides (*N*-acylenamines) give rise to a plethora of reactions in the excited state. Thus, simple enamides such as *(1)* rearrange photochemically to vinylogous amides *(2)*. Dienamides undergo photocyclization to complicated heterocycles, *e.g.* with benzylisoquinoline or indole alkaloid skeletons; these reactions can facilitate the synthesis of natural products. [The



(1) *(2)*

R = C_6H_5, CH_3; R′ = C_6H_5

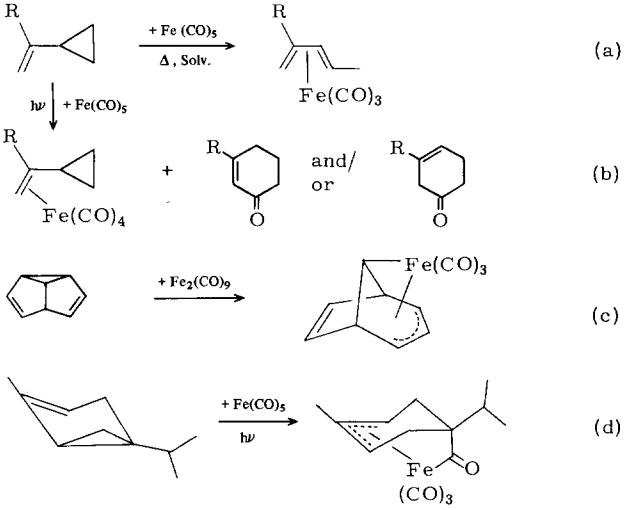
Photochemistry of Enamides. Synthesis *1978*, 489–518; 143 references]

[Rd 34 IE]

The linkage between teichoic acid and peptidoglycan in bacterial cell walls is dealt with in an article by *J. Coley, E. Tarelli, A. R. Archibald*, and *J. Baddiley*. Although teichoic acid can be extracted from cell wall specimens and thus separated from totally insoluble peptidoglycan, the interaction between both cell wall components is not of a purely electrostatic nature but also involves covalent bonding. The acid-labile *N*-acetylglucosamine-1-phosphate bond and an alkali-labile phosphodiester bond between the alcohol and the sugar component were recognized as covalent bonds participating in the linking. The presence of the same type of or similar linkage sites in cell walls of otherwise quite different structure would suggest that various species use the same mechanism for the linkage of both cell wall components. [The Linkage between Teichoic Acid and Peptidoglycan in Bacterial Cell walls. FEBS Lett. *88*, 1—9 (1978); 37 references]

[Rd 27 IE]

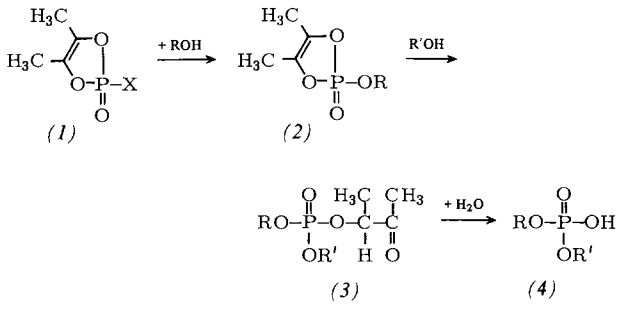
Metal-induced rearrangements and insertions into vinylcyclopropanes and related compounds are described by *S. Sarel*. Vinylcyclopropanes can undergo four types of reaction with carbonyliron compounds (a—d). $Fe(CO)_5$ was found to be



an effective "homodienophile", and vinyl- and divinylcyclopropanes were recognized as a new source of 4 and 6 π electrons suitable for coordination to metals. [Metal-Induced Rearrangements and Insertions in Cyclopropyl Olefins. Acc. Chem. Res. *11*, 204—211 (1978); 44 references]

[Rd 32 IE]

Phosphorylation by means of cyclic enediol phosphates, *(1)*, X = *e.g.* Cl, is the title of a review by *F. Ramirez* and *J. F. Marecek*. The synthesis of phosphoric diesters of type *(4)* from the alcohols ROH and R′OH and the enediol phosphate *(1)* has the advantage that the cyclic phosphates are very reactive, that the reaction step *(2)* → *(3)* is effectively catalyzed by, *e.g.*, imidazole or triethylamine, and that the formation of symmetrical diesters by transesterification is suppressed.



The pyrophosphate derived from *(1)* is suitable for the synthesis of, *e.g.*, deoxyribooligonucleotides and phospholipids. [Phosphorylation by Means of Cyclic Enediol Phosphates. Acc. Chem. Res. *11*, 239—245 (1978); 47 references]

[Rd 35 IE]

Transport durch biologische Membranen. (Transport Across Biological Membranes.) By *M. Höfer*. Verlag Chemie GmbH, Weinheim—New York, 1977. 1st edit., ix, 128 pp., 49 figs., 6 tables, paperback, DM 44.00.

The author has given a condensed account—long outstanding in German—of the current knowledge of transport of molecules across biological membranes, permitting the reader to gain a quick access to this already very extensive field.

The work deals mainly with the kinetic and theoretical aspects of membrane transport, which reflects the trend in transport research so far. The structure of the membrane is considered a black box, and the concentrations of ions or metabolites, or changes in these, are measured on both sides of the membrane. Only in the last few years has one started to isolate the molecular components making up the transport system.

The transport across biological membranes is treated in five chapters: 1. Structure and function of biological membranes, 2. The transport function of biological membranes (*e.g.* basic laws, diffusion of ions, and carrier-based transport), 3. Kinetics of catalyzed transport (*e.g.* transport kinetics under equilibrium conditions, kinetics of counter-transport, carrier-based transport and diffusion, and inhibition of transport processes), 4. Active transport processes (*e.g.* the phosphotransferase system in bacteria, sodium pumps, chemiosmotic theory, kinetics of active carrier-based transport), and 5. Molecular foundations of carrier-based transport (*e.g.* carrier molecules, problems of carrier isolation, ionophores, and reconstitution of transport systems). The derivation of kinetic equations and the necessary mathematics are described in detail in an appendix.

The book is mainly oriented at kinetics, therefore some of the experimental problems are not discussed: how to isolate membrane vesicles, how to find out whether these are open or closed, and the question of whether the isolation alters the permeation characteristics of eukaryotic membranes. Similarly, when discussing the current membrane models, the author restricts his presentation to the polymer membrane model, for which not much experimental evidence exists. *Singer* and *Nicolson*'s fluid mosaic model, now accepted by most research workers, is not presented, and literature references for it are also missing.

To sum up, the book gives a condensed and well-organized account of the broad subject of membrane transport and gives the experimental examples which are known up till now. The main emphasis is on kinetics and mathematical treatment. The book makes it possible to gain a quick introduction to the problems of transport across bio-membranes, and it is to be welcomed.

G. Brunner [NB 424 IE]

Basis-Römpp. Taschen-Lexikon der Chemie, ihrer Randgebiete und Hilfswissenschaften (Pocket Dictionary of Chemistry and Related Fields). By *O.-A. Neumüller*. Franckh'sche Verlagshandlung, Stuttgart, 1977. 1st edit., vol. 1: A—L, vol. 2: M—Z, altogether 768 pp., numerous figures, boards, DM 39.50.

Certainly not everybody who needs the big six-volume Römpp for his work has it, either because of the cost or because of the very space it takes up. It was therefore an obvious and sensible idea to produce a "distillate" from the complete version. The result is the Basis-Römpp, which consists of a selection of the entries found in the well-established Chemie-Lexikon. The entries selected for the pocket edition relate to important fundamental concepts of chemistry, classes of compounds like aldehydes, nucleic acids, and metals, types of reactions, measurement methods and methods of investigation, and laws. The entries have the same text as in the parent work, so there is no loss of quality—only the literature at the end of the entries has been omitted to save space. This version does not give *e.g.* commercial products, trivial names, and single compounds. The elements are mentioned only under the heading of the Periodic System and are not discussed where they should come in an alphabetical arrangement. This means that they are not covered, and they may be missed by some non-chemists—*e.g.* medics, biologists and physicists—who are among those for whom the book is intended; chemists at universities and in industry can overlook this, because they will find suffucient information on the elements in other reference books. Of course, we cannot ask for everything when the price is so low. As a handy reference book the Basis Römpp certainly achieves its objective; those who want to know more are referred to the sources taken over from the big Römpp.

C. Weiske [NB 423 IE]

Comprehensive Biochemistry. Vol. 25: Regulatory Functions—Mechanisms of Hormone Action. Edited by *M. Florkin* and *E. H. Stotz*. Elsevier/North Holland Biomedical Press, Amsterdam, 1975. 1st edit., 199 pp., 22 figs., 12 tables, bound, Dfl. 40.00.

When reviewing a book published three years ago one can either mention what has happened since to make the book obsolete or to treat it as a document. In the second case the book under discussion ought to be compared with volume 24. The new volume treats the mechanisms of hormone action and the characteristics and functions of adenylate-cyclases, both under the general heading of "biochemical regulation". The subject is divided into compartments by the cell membrane, being concerned with what happens on the two sides of the cell membrane and in it. Both chapters therefore deal with very topical subjects and, as always when a subject has a future, the work has its own noncooperative evolutionary mechanisms and corresponding non-linear publication kinetics.

In the first chapter *P. Karlson, B. Doenecke*, and *C. E. Sekeris* discuss—on the basis of over 400 references, covering the field up to 1974—the interactions of steroid, thyroid, and peptide hormones with components of the cytoplasm and the nucleus, particularly with chromatin. Adenylate-cyclase systems are thus deliberately treated separately in the next chapter. The authors first cite the experimental observations and then weigh up the merits and the shortcomings of the various interpretations, hypotheses, and theories—and mostly reject them. The most likely interpretation is that the signal substances are bound on a chromatic protein, and this initiates the transcription by RNA polymerase B. The chapter is distinguished by exemplary clarity and critical systematization and is a good, stimulating contribution to a handbook.

E. W. Sutherland made the very important discovery that cyclo-AMP is a secondary messenger, which takes the cell-spe-

cific information coming from catecholamines and hydrophilic hormones and picked up by the membrane receptors, conveys it to protein-kinases by a subcellular mechanism, and regulates enzymatic activities by the modification of enzymes. This feature separates these classes of hormones from the above-mentioned steroid hormones, which have a direct action. In the description of the adenylate-cyclase system, *T. Braun* and *L. Birnbaumer* discuss in detail how the reaction of a hormone with its exo-membrane receptor leads to the activation of the cyclase (mentioning 200 references up to 1973). Despite new data about details, this explanation is basically still valid. However, we have since come much closer to the characterization of the specific receptors and modification reactions. The authors are commendably selective and have refrained from using the very convincing cyclo-AMP-sensitive biological process as a supporting model. In all, this chapter leaves little to desire even after three years, so that the present volume maintains the standard we have come to expect of this series[*]. Unfortunately, the readers should be warned that the series is slow in reaching completion and that many supplementary volumes are still to come.

L. Jaenicke [NB 428 IE]

Developments in Food Carbohydrate—1. Edited by *G. G. Birch* and *R. S. Shallenberger*. Applied Science Publishers Ltd., London, 1977. 1st edit., x, 189 pp., 58 figs., 51 tables, bound, $ 25.00.

This first volume in a series of concise monographs on recent developments and advances in topical areas of carbohydrate research in the field of nutrition science contains ten contributions, most of which were originally given as papers at an ACS Symposium by the Division of Carbohydrate Chemistry and Agricultural Food Chemistry. They deal with new theoretical and practical data on the structure and properties of sugars and polysaccharides, metabolic and biochemical relationships, biological functions, analyses, and points of technology and nutrition physiology.

More specifically, *G. Birch*'s contribution deals with the chemistry and properties of glucose syrups (19 pages), and *M. Seidman*'s with the particularly topical subject of the technological development of fructose manufacture (24 pages). *S. Arnott* describes investigations of the states of order in gel-forming polysaccharides by the X-ray crystallographic analysis of oriented fiber structures (18 pages). The next two contributions deal with the occurrence, biosynthesis, and functions of heptuloses (by *E. A. McComb* and *V. V. Rendig*, 16 pages) and with the raw materials and the method used in lactose production (by *T. A. Nickerson*, 14 pages). Special topics are covered by the next sections: nonenzymatic browning in orange juices (*P. Shaw*, *J. Tatum*, and *R. Berry*, 22 pages), the effect of carbohydrates on intestinal transport and enzymatic activities in rats (*S. Reiser*, 28 pages), the solubilities of starch fractions in the cooking of rice (*R. J. Priestley*, 16 pages), the connection between food quality and carbohydrate dehydration reactions (*M. S. Feather*, 16 pages), and the production of biscuits with a reduced risk of causing caries (*T. Grenby* and *J. Bull*, 16 pages).

The contributions are written by competent writers, contain a large number of literature references, and provide what must certainly be a large circle of interested people with useful information and ideas.

K. Heyns [NB 421 IE]

[*] Cf. Angew. Chem. Int. Ed. Engl. *15*, 178 (1976).

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

The Porphyrins, Vol. 2. Structure and Synthesis, Part B. Edited by *D. Dolphin*. Academic Press, New York 1978. xix, 437 pp., bound, $ 46.50.—ISBN 0-12-220102-7

Treatise on Analytical Chemistry. Part II. Analytical Chemistry of Inorganic and Organic Compounds. Vol. 10. Edited by *I. M. Kolthoff*, *Ph. J. Elving*, and *E. B. Sandell*. John Wiley & Sons, New York 1978. xviii, 566 pp., bound, $ 43.85.—ISBN 0-471-49998-6

Organic Chemistry of Iron, Vol. 1. Edited by *E. A. Koerner von Gustorf* (deceased), *F.-W. Grevels*, and *I. Fischler*, Academic Press, New York 1978. xii, 673 pp., bound, $ 29.50.—ISBN 0-12-417101-X

The Chemistry of Nonaqueous Solvents, Vol. 5A. Principles and Basic Solvents. Edited by *J. J. Lagowski*. Academic Press, New York 1978. xvii, 297 pp., bound, $ 31.00.—ISBN 0-12-433805-4

Systematic Materials Analysis, Vol. 4. Edited by *J. H. Richardson* and *R. V. Peterson*. Academic Press, New York 1978. xviii, 493 pp., bound, $ 49.50.—ISBN 0-12-587804-4

Fracture Mechanics of Ceramics, Vol. 3. Flaws and Testing. Edited by *R. C. Bradt*, *D. P. H. Hasselman*, and *F. F. Lange*. Plenum Press, New York 1978. xxii, 506 pp., bound, $ 54.00.—ISBN 0-306-37593-1

Fracture Mechanics of Ceramics, Vol. 4. Crack Growth and Microstructure. Edited by *R. C. Bradt*, *D. P. H. Hasselman*, and *F. F. Lange*. Plenum Press, New York 1978. xiii, 998 pp., bound, $ 54.00.—ISBN 0-306-37594-4

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Extraction with Supercritical Gases—A Foreword

By Günther Wilke[*]

A comparative study of the diverse operations of chemical synthesis and analysis quickly reveals the paramount importance of separation steps. Any synthesis affords mixtures, and the desired product usually has to be separated from by-products and auxiliary materials—whether it is formed *in vitro* or *in vivo*. Analysis is based primarily on separations. These trivial statements would suggest that during the development of chemistry the fundamental methods of separation have long been recognized and mastered. It is therefore all the more astonishing that the first symposium on a novel method of separation, *viz.* extraction with supercritical gases[**], was held this year. In simplified terms, this new method is characterized by the following features:

1) Relatively involatile materials can be dissolved by supercritical gases—sometimes even selectively—to form a charged supercritical phase.

2) Phenomena of distillation and extraction are utilized simultaneously, *i.e.* enhancement of vapor pressure and phase separation both play a role.

3) The properties of the extracting agent, and especially its density, can be varied within wide limits by means of pressure and temperature.

4) Separation of the dissolved substances can be accomplished either by reducing the pressure (at constant temperature) or by raising the temperature (at constant pressure).

The first observations that solids such as metal halides are soluble in ethanol or tetrachloromethane under conditions above the critical point (C_2H_5OH: $T_c = 243\,°C$, $P_c = 63$ atm; CCl_4: $T_c = 283\,°C$, $P_c = 45$ atm) date back to 1879[1]. It was also known at an early date that hydrocarbons are entrained in highly compressed natural gas during the winning of petroleum[2]. Even purely academic studies on well-defined multicomponent systems, *e.g.* the methane/*n*-decane system, have long been available[3]. It appears, however, that no chemical engineering applications were initially considered apart from technically impractical proposals[4] and a process corresponding to liquid-liquid extraction which happens to employ a supercritical gas[5].

As is so often the case, it was a simple and, in fact, misinterpreted observation that initiated the development of new separation process. In view of discussions on research-planning it seems appropriate to retrace the course of such developments and to demonstrate on the basis of the known motivations that it is in general the careful observation of the unexpected which marks the beginning of significant new advances in knowledge and not theoretical predictions. However, only the correct conclusions drawn from the observation lead ultimately to success. Although this is trivial, it is a far from trivial matter to draw such conclusions.

The route leading from the chance individual observation to the now imminent industrial commercialization of separation with supercritical gases is described in the first of the following essays. *Zosel* began his fundamental studies as early as 1962 at the Max-Planck-Institut für Kohlenforschung and has since developed a general industrial process[6]. In 1970 he discovered the decaffeination of green coffee with the pharmacologically completely acceptable carbon dioxide[7] which is to come on stream this year. *Vitzthum* and *Hubert* investigated other applications to the isolation of natural products and these too have already attracted industrial interest.

That the physicochemical principles underlying the novel method are highly sophisticated, although the process was developed with a fair degree of intuition, follows from the

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[**] This symposium was held on 5 and 6 June, 1978, at "Haus der Technik", Essen, an external department of the Technische Hochschule Aachen. Joint chairmen were *G. M. Schneider* (Bochum), *E. Stahl* (Saarbrücken), and *G. Wilke* (Mülheim-Ruhr).

contribution by *Schneider*. The study of binary mixtures of polar components such as water or ammonia with nonpolar substances such as hydrocarbons in the critical range is also based on physicochemical measurement (*Lentz* and *Franck*). The extractability of natural products in particular can be assessed with great facility and speed by using supercritical gases in the elegant chromatographic microanalysis developed by *Stahl*. Practical possibilities and the theoretical basis of chromatography with supercritical gases are discussed by *Klesper* who was responsible for the first application of such systems to gas chromatography[8].

Peter and *Brunner* have studied the separation of relatively involatile substances with compressed gases in a countercurrent process and have already made calculations for a large-scale plant. The approach to the design of such plants is discussed by *Eggers*; the high-pressure systems necessarily involve a certain degree of sophistication.

It is no coincidence that all the authors of the progress reports published in this issue come from West Germany, since it is here that the separation process was discovered and developed. For the sake of completeness, however, it should be mentioned that the extraction of coal with supercritical solvents such as toluene ($T_c = 320\,°C$, $P_c = 41.6$ atm) has been studied in Great Britain since about 1970 with the support of the National Coal Board[9]. Under these extreme conditions (350 °C) up to about 30 % of the coal can be extracted. The solvent-free extract contains more hydrogen than the coal (6.9 % instead of 4.9 %) and could be used in the production of hydrocarbon oils and as a chemical raw material. The economics of the process appear somewhat questionable.

Numerous scientists from abroad also attended the Essen symposium and a general summary might be: the separation of substances with supercritical gases will probably find numerous further applications in the years to come.

Received: July 27, 1978 [A 241 IE]
German version: Angew. Chem. 90, 747 (1978)

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[6] *K. Zosel*, US-Pat. 3969196 (Priority: April 16, 1963), Studiengesellschaft Kohle.
[7] *K. Zosel*, DBP 2005293 (Priority: Feb. 5, 1970), Studiengesellschaft Kohle.
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[9] *W. S. Wise*, Chem. Ind. (London) *1970*, 950; *J. C. Whitehead, D. F. Williams*, J. Inst. Fuel *1975*, 182; *K. D. Bartle, T. G. Martin, D. F. Williams*, Fuel *54*, 226 (1975).

Separation with Supercritical Gases: Practical Applications[**]

By K. Zosel[*]

Extraction with supercritical gases combines, to a certain extent, the characteristics of both distillation and extraction; the term "destraction" is therefore proposed for this method of separation. The principles of the method are illustrated in this article by a series of color photographs comparing extraction and destraction. Of the practical uses of this new method may be mentioned the separation of cod-liver oil into 50 fractions, each differing in saponification value and iodine number, by means of supercritical ethane and, in particular, the decaffeination of raw coffee with supercritical carbon dioxide.

1. Introduction

Development of the technique of separating substances using supercritical gases first began in the early 60's[1], though certain fundamental principles had already been known for more than 80 years[2] and experimental results seemingly anticipating the potential of this new principle were first reported in the 50's[3]. What really initiated the development of this new method of separation? It is instructive to follow the progress of this development in connection with research-planning and to show by reconstructing the course of events that, in general, it is the careful observation of an unexpected, and hence presumably seldom theoretically predictable behavior, which initiates significant new trends.

In the early 1950's *Ziegler* and *Gellert*[4] discovered the so-called "Aufbau" reaction of triethylaluminum with ethylene under pressure at *ca.* 100 °C—a reaction which today forms the basis of the large-scale preparation of long-chain primary alcohols *(1)* for conversion into biodegradable detergents.

$$\text{al-}C_2H_5 + x\,C_2H_4 \longrightarrow \text{al-}(C_2H_4)_x\text{-}C_2H_5 \xrightarrow{1/2\,O_2}$$

$$\text{al-O-}(C_2H_4)\text{-}C_2H_5 \xrightarrow[-\text{alOH}]{H_2O} HO\text{-}(C_2H_4)_x\text{-}C_2H_5 \qquad (1)$$

al = 1/3 Al

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[**] Based on a lecture delivered at the Symposium on "Extraction with Supercritical Gases", June 5, 1978 in Essen (Germany).

This reaction was carried out on a laboratory scale as follows: a 200 ml autoclave was charged with *ca.* 10 ml of triethylaluminum (b.p. 194 °C/760 torr) and filled with ethylene at room temperature. Under these conditions the ethylene is 10—15 °C above its critical temperature ($T_c = +9$ °C). In this temperature range the compressibility of ethylene is particularly high, so the pressure cannot be used as a guide for the amount in the autoclave: this was determined by weighing. In one case it was found that the autoclave was overfull, and heating to 100 °C would have resulted in too high a pressure. It seemed inadvisable to simply vent the autoclave since it was feared that traces of the spontaneously inflammable triethylaluminum might be carried over and ignite the gas. The gas was therefore vented through a cold trap, where condensation of $Al(Et)_3$ was indeed observed. It was assumed that this had been carried over either in the form of droplets or that it had crept up the sides of the autoclave. This phenomenon did not receive further attention.

A systematic investigation of the ability of pressurized ethylene to transport high-boiling material was first undertaken in 1962 as the result of a difference of opinion with a licensee concerning the quality of the product of the "Aufbau" reaction. The product prepared by the licensee contained large quantities of α-olefins which were virtually absent from our product obtained under the same conditions. The α-olefins *(2)* are produced in a side reaction in which, at 100–120 °C, the trialkylaluminum undergoes cleavage to give dialkylaluminum hydride and an α-olefin[5].

$$\text{al-CH}_2\text{-CH}_2\text{-R} \longrightarrow \text{alH} + \text{CH}_2\text{=CH-R} \qquad (2)$$

al = 1/3 Al

The controversial results arose from differences in the experimental procedures. In our experiments the α-olefins formed were removed from the reactor by the supercritical ethylene and hence separated from the "Aufbau" product. This effect could not be associated with the partial pressure of the α-olefin since this was far too low. The procedure used by the licensee, however, did not lead to this separation. It was very quickly realized that a general principle had been discovered for the separation of substances.

2. Phenomenological Considerations

Distillation and extraction are among the most important separation procedures. Whereas separation by distillation is based upon the different vapor pressures of the components, separation by extraction is based on those properties of the material which determine the intermolecular interaction with the molecules of the extraction agent. Both of these effects are, to a certain extent, united in the general process described above for the separation with the help of supercritical gases, and for this reason the expression *destraction*[*] is proposed.

It has been known for some time that liquified gases can be used as solvents, *i.e.* as extraction agents, in liquid-liquid extraction. One of the most important technical applications is in the deasphalting of petroleum with propane[6]. The characteristic differences between an extraction of this type and destraction can be convincingly illustrated using this process as an example.

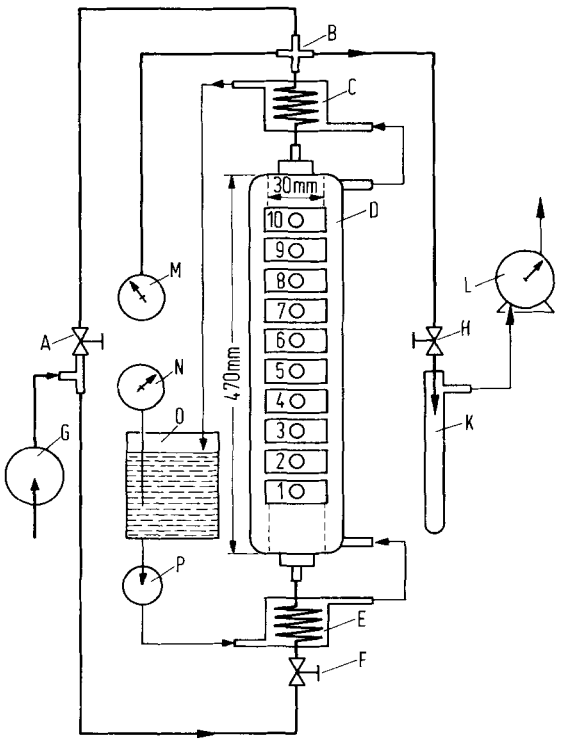


Fig. 1. Thermostated custom-built autoclave (schematic) C, D, E, O, P = pumps, A, F = inlet valves, H = outlet valve for product and gas, G = reservoir for product and gas, L = gas meter for measuring volume of decompressed gas, M = manometer, N = thermometer, B = splitter, *1–10* = glass windows.

A schematic diagram of the apparatus used for this experiment is shown in Figure 1. A custom-built autoclave consisting of a thermostated vertical pressure vessel furnished with 10 glass windows at the front and the rear was used, thus enabling processes occurring inside the autoclave to be observed directly. The autoclave has a volume of *ca.* 450 ml.

The series of pictures in Figure 2 illustrate a typical propane extraction of the top-residue of a petroleum distillation. The extraction conditions in Figures 2a and 2b correspond exactly to those used by *Zhuse*[3] (*i.e.* 105 °C, 8° above T_c, 100 atm, $\rho \approx 0.379\ g\,cm^{-1}$[**]). As mentioned in the introduction, these conditions seem, at a first glance, to have anticipated the principle of destraction.

Fig. 2. Photographs of part of the autoclave shown schematically in Fig. 1 (windows 1—10, manometer M, thermometer N, receiver K) during treatment of petroleum top-residues with propane. a), b) Extraction under the conditions used by *Zhuse* [3]: 105 °C (8° above T_c), 100 atm, $\rho \approx 0.37\ g\,cm^{-3}$. c), d) Destraction at 140 °C (43° above T_c), 100 atm, $\rho \approx 0.29\ g\,cm^{-3}$ (see color plate, p. 705).

Initially the top-residue meniscus appears in the second window (Fig. 2a above, left). Propane is fed in, dissolves, and the level of the meniscus rises (windows 2—9). On reaching a particular composition (with the meniscus in window 9 Fig. 2a below, right) a sudden demixing occurs and a second

[*] From the Latin *destillare* and *extrahere*.

[**] In the following discussion the density of the pure gases as taken from tables are cited. It should be noted that these are not the densities of the loaded phase.

meniscus forms, *i.e.* at this stage the following phases are present: a dark liquid (windows 1—4), a red liquid (windows 4—9), and a practically colorless gas phase (windows 9 and 10, Fig. 2b above, left). Removal of gas at constant pressure through valve H (additional propane is fed in through valve F) causes the second meniscus to rise further (Fig. 2b, above right) until finally a dark, extracted oil is carried over into K. This is accompanied by a fall in the level of the meniscus of the dark phase (window 5 to window 3).

Figures 2c and 2d show the situation at 140 °C (43° above T_c) and 100 atm ($\rho \approx 0.29\,g\,cm^{-3}$). The initial behavior in Figure 2c, in which a liquid and a gas phase are observed, is similar to that Figure 2a, and the dark phase rises from window 2 to window 5.

The basic difference between extraction and destraction becomes clear in the stages which follow: a light, transparent loaded supercritical gas phase is formed in addition to the liquid phase (windows 5—10) *without* the formation of a second liquid phase (Fig. 2d). The removal of this gas phase through the valve H leads to the isolation of pale yellow destracted oil in K. There is a basic difference between the phase behavior and the selectivity in the two cases, which makes itself apparent in the color of the transported product. Both systems also show a characteristic difference in their response to slight decompression: gas bubbles are formed (particularly in the upper phase) in the system having two liquid phases (Fig. 2b), *i.e.* boiling occurs, whereas in the second system (Fig. 2d) turbidity in the gas phase is observed as a result of phase separation, thus indicating that a true supercritical phase has been generated. The top-residue destraction will be discussed in more detail in Section 4. A number of characteristic phenomena will now be discussed. If ethylene is bubbled through paraffin oil at room temperature (23 °C, *i.e.* 14 °C above T_c) and atmospheric pressure ($\rho \approx 0.0013\,g\,cm^{-3}$) 100 g of ethylene transport *ca.* 0.1 g of oil. On raising the pressure, the amount of oil transported per 100 g of ethylene hardly changes until the critical pressure ($P_c = 50$ atm, $\rho \approx 0.22\,g\,cm^{-3}$) is reached; at this point a dramatic increase in the amount of oil transported is observed, and at 200 atm ($\rho \approx 0.4\,g\,cm^{-3}$) 100 g of ethylene transport *ca.* 25 g of paraffin oil. At 200 atm and 70 °C ($\rho \approx 0.32\,g\,cm^{-3}$) the value falls to *ca.* 7 g. These effects can be interpreted to a first approximation as follows: The amount transported at atmospheric pressure corresponds roughly to that expected from the partial pressure of the paraffin oil. As the pressure rises, the solubility of ethylene in the oil increases and is accompanied, at most, by an insignificant increase in the partial pressure as a result of changes in the intermolecular forces. At and just above the critical pressure, the density of the gas increases dramatically as a result of the increased compressibility (as mentioned in the introduction, the pressure in this case says little about the degree of packing, *i.e.* the density). The high density gas is now able to take up large quantities of oil and a loaded supercritical gas phase is formed. Raising the temperature from 23 °C to 70 °C at constant pressure (200 atm) leads to a decrease both in density and in the ability of the gas to transport oil. If, however, the temperature is increased while keeping the density constant (by increasing the pressure) then the ability of the gas to take up oil also increases. The large increase in the density above the critical pressure is also accompanied by a dramatic increase in the solubility of the gas in the liquid phase. This facilitates transfer of the oil into the supercritical gas phase.

3. Fractionation

The observation that an increase in temperature at constant pressure is accompanied by a decrease in density and hence in the ability to transport material, forms the basis of an important application: mixtures of high boiling material, which are not amenable to fractional distillation, can be separated. This principle is illustrated in the series of pictures shown in Figure 3.

Fig. 3. Photographs of part of the autoclave shown schematically in Fig. 1 (modified; windows 1—10 (not numbered), manometer M, thermometer N, variable temperature finger) during treatment of a mixture of α-olefins (C_{14}—C_{20}) with supercritical ethylene. a)—f) see text (see color plate, p. 708).

The autoclave shown in Figures 1 and 2 has been fitted with a variable temperature finger and is charged at 25 °C (16 °C above T_c for ethylene) with 100 ml of a mixture of high boiling α-olefins (C_{14}—C_{20}) (Fig. 3a, the meniscus can be seen in the third window). On pressurizing with ethylene, the gas dissolves in the liquid and the level of the meniscus rises. At the critical pressure (*ca.* 50 atm, $\rho \approx 0.22\,g\,cm^{-3}$) a fog forms above the meniscus which is now in the 4th window (Fig. 3b)[*].

The fog disappears on raising the pressure and at *ca.* 70 atm ($\rho \approx 0.24\,g\,cm^{-3}$), the volume of the liquid has increased threefold (Fig. 3c, meniscus in window 6).

Product is now removed from the supercritical phase at constant pressure and depressurized. The olefin mixture is collected and the level of the meniscus falls (Fig. 3d).

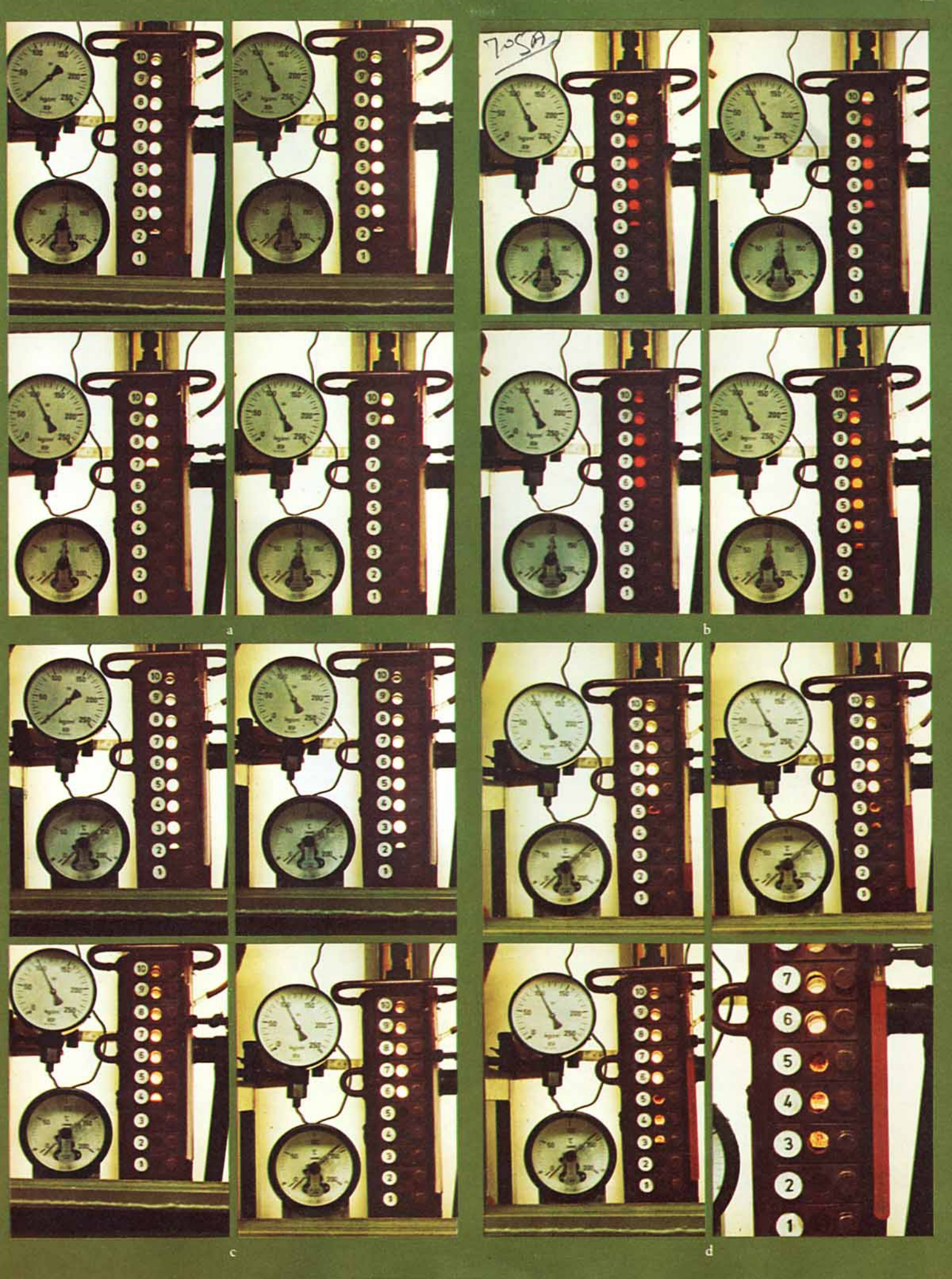
Formation of a fog is also observed if the pressure is suddenly decreased by a few atmospheres (Fig. 3e, window 6—9). The liquid droplets that are formed fall back into the liquid phase.

Condensation of the olefin mixture present in the supercritical phase can also be brought about at constant pressure by increasing the temperature of the finger to 35 °C, *i.e.* 10° above the temperature of the rest of the system. Droplets form on the tip of the finger and then fall through the supercritical phase back into the liquid phase (Fig. 3f). The result is vigorous refluxing.

This phenomenon has been exploited to effect a fractionation. The apparatus (Fig. 4), which consists of a still (25 l), a column and a heated finger, was charged with a mixture of α-olefins (traces C_{14}, 21 C_{16}, 21 C_{18}, and 71 C_{20}), and fractionated with ethane ($T_c = 32$ °C, $P_c = 48$ atm) at 45 °C and an initial pressure of 60 atm ($\rho \approx 0.2\,g\,cm^{-3}$) with a finger temperature of 85 °C ($\rho \approx 0.08\,g\,cm^{-3}$). The supercritical ethane-olefin phase passes through the column, which is filled with copper rings, and reaches the hot finger where refluxing

[*] The same effect is observed in lecture demonstrations for the transition of CO_2 from the liquid to the supercritical condition by warming a thick-walled, sealed glass tube filled with CO_2.

Figure caption to the color plate on facing page (Fig. 2). is on p. 703.


a
b
c
d

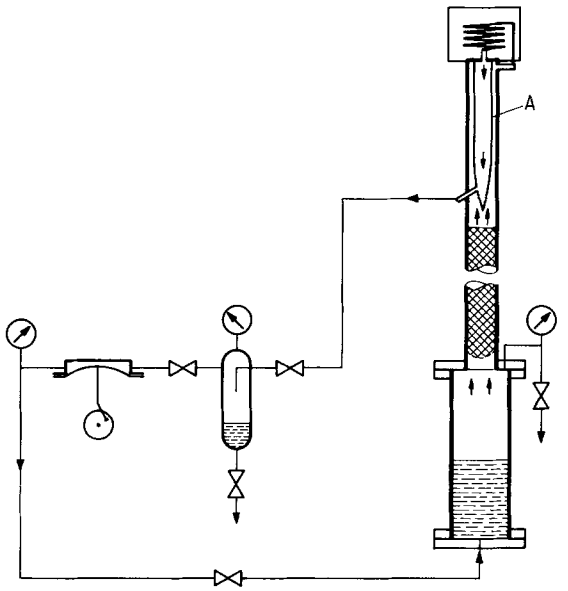


Fig. 4. Apparatus for fractional destraction (schematic, not to scale). For explanation see text. A = variable temperature finger.

occurs. The supercritical gas is bled off and partially depressurized to 30 atm ($\rho \approx 0.03$—$0.04\,g\,cm^{-3}$). The product separates out and is collected (60 ml/h). The gas is then repressurized. The pressure is slowly increased during the destraction from 60 atm to 110 atm ($\rho \approx 0.35\,g\,cm^{-3}$). (Increasing the pressure in a destraction is analogous to raising the temperature during a distillation.) A GC-analysis of the various fractions shows that a successful separation has been accomplished; *e.g.* a fraction containing *ca.* 25% of the C_{16}-olefin has a purity of 95.5%.

Since the components and the gas are aliphatic hydrocarbons this separation is based primarily on the differences in vapor pressure of the components and thus resembles a distillation *i.e.* the components are taken up into the gas phase in the order of their increasing boiling points. This effect can be overlapped by a separation according to the class of compound in those cases in which certain components in the mixture have, for example, little affinity for the supercritical gas while others are taken up preferentially. Distillation and extraction then combine together as destraction.

According to our experience effective destraction can be obtained in a temperature range of 10 to 100°C above the critical temperature of the gas being used and in a pressure range of 50—300 atm. Gases which are particularly effective are those whose critical temperatures are neither extremely high nor extremely low. We have obtained satisfactory results with the following gases: ethane (T_c 32°C, P_c 48 atm), ethylene (T_c 9°C, P_c 50 atm), propane (T_c 97°C, P_c 42 atm), propene (T_c 92°C, P_c 46 atm), CO_2 (T_c 31°C, P_c 73 atm) and NH_3 (T_c 132°C, P_c 111 atm). NO and N_2O can also be used but care must be taken since explosions can occur, particularly in the latter case. Destraction will be the method of choice in cases where separation can otherwise only be carried out by vacuum distillation or particularly where even this is ineffective due to decomposition of the material at the distillation temperature. The process should be of particular interest to the oil industry and to the food industry.

4. Practical Applications

The destraction of top-residues which we have mentioned in the introduction to illustrate the principles involved, has been run as a continuous process in a pilot plant. The flow sheet is shown in Figure 5.

The starting material is stored in a 750 l reservoir at 95°C from where it is pumped through a measuring vessel into a T-piece and mixed with propane at 130 atm. The propane is preheated in a horizontal heat exchanger. The mixture enters a tilted destractor which is kept at 140°C where it separates into a supercritical gas phase and destracted top residue. The former is removed at the top of the packed bed while the latter is collected in a separator and, after decompression in a degasser, is removed as asphalt. The loaded supercritical gas phase is partially depressurized to 125 atm, whereby a small quantity of destract separates out and is recirculated. The main destract is isolated by reducing the pressure to 30 atm followed by degassing at 0.3 atm. The gas liberated at various stages is recompressed, passed through the heat exchanger and recirculated. It is obvious that all the tubing must be heated and well insulated. 75% of the starting material is isolated as destract—the remainder is asphalt and contains most of the vanadium. Additional vanadium separates out during the pressure drop from 130 atm to 125 atm.

A liquid-liquid extraction using propane at 70°C was carried out for comparison and in order to demonstrate the particular advantages of destraction. In this case also, 75% of the starting material could be separated. The products, however, differ significantly in important analytical data: the destract has a much lower vanadium content (0.15 ppm compared to 2.4 ppm in the extract) and a more favorable Conradson number (1.3 compared to 2.0). The Conradson number is a measure of the amount of involatile material present. The low vanadium value is particularly significant should the product be used as fuel to drive a gas-turbine, since vanadium as V_2O_5 is highly corrosive.

Even more impressive is the fractionation of cod-liver oil. The separation was carried out in an apparatus similar to that used to separate the C_{16}–C_{20} α-olefins (Fig. 4). 20 kg of starting material were separated into 50 fractions using supercritical ethane at 100—160 atm with a still temperature of 27°C, a column temperature of 50°C and a finger temperature of 90°C. The fractions were characterized by their saponification values and iodine numbers. (The first is associated with the molecular weight and the second with the degree of unsaturation of the fraction.) The correlation between these values for the various fractions is shown in Figure 6.

The curve is made up of 50 points corresponding to the fractions and is related to a distillation curve. It is almost unnecessary to mention that fractionation of components having such high molecular weights as the triglycerides is impossible using conventional distillation techniques.

This last example shows that destraction can be carried out at relatively low temperatures which predestinates the method for the separation of thermally labile substances. It is for this reason that destraction has received considerable attention in the last few years from the food industries, for it is possible, for example, to remove fats and oils from vegetable

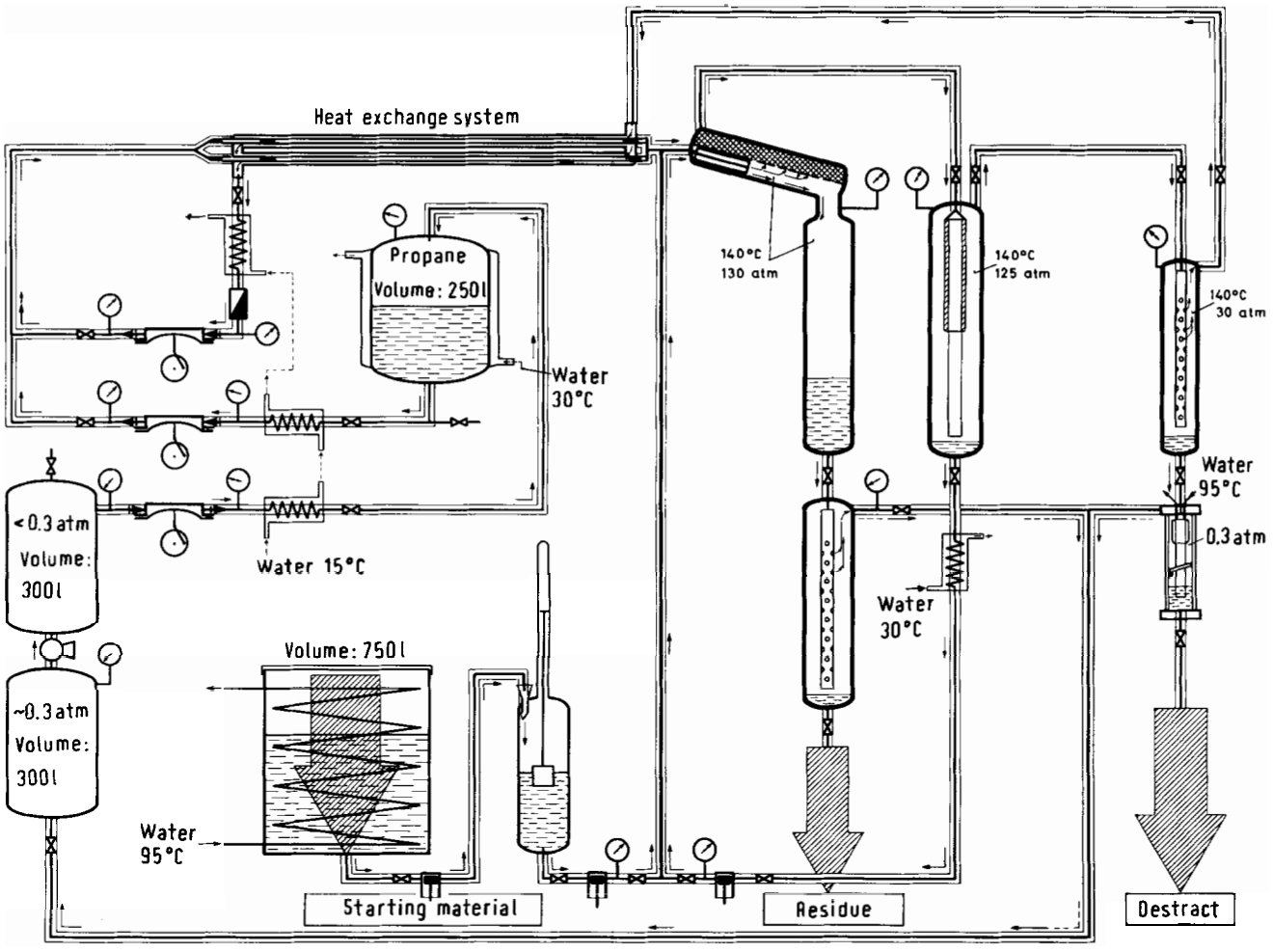


Fig. 5. Flow sheet of a pilot plant for continuous destraction of petroleum top-residues with propane.

and animal matter under mild conditions without the necessity of a final step in which solvent is removed. A variation of the procedure is to extract the desired product under subcritical conditions, *i. e.* using a liquid gas, and then separate the extract into its components under supercritical conditions. It has proved possible to remove cocoa butter from cocoa beans, soybean oil from soybeans as well as the essential oils from spices. In addition alkaloids can be removed from plants, *e.g.* nicotine from tocacco.

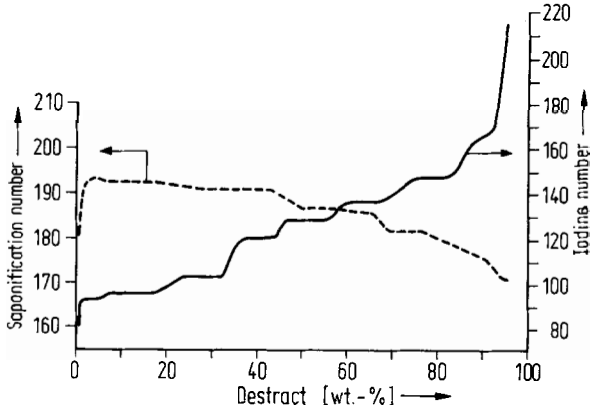
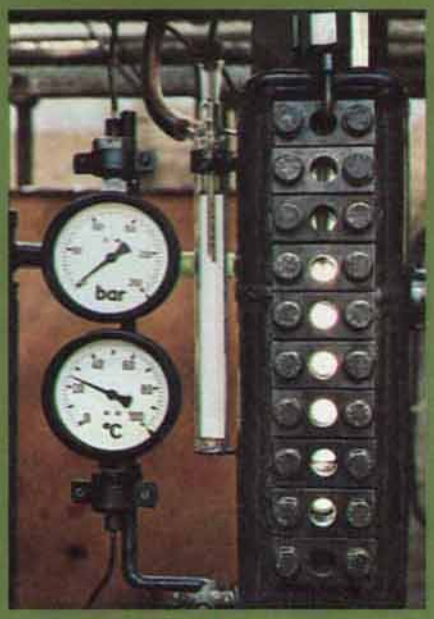


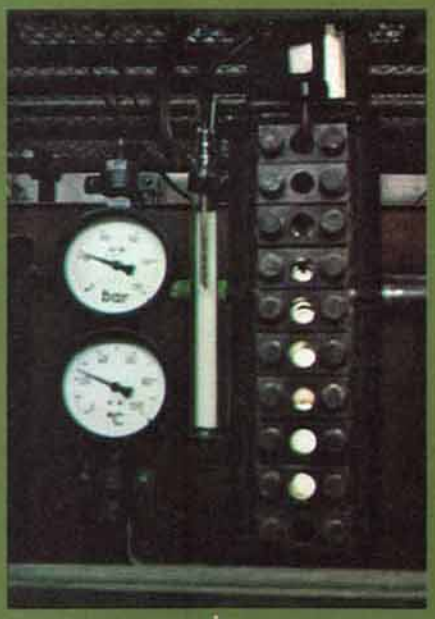
Fig. 6. Fractional destraction of cod-liver oil using the apparatus shown in Figure 4.

In conclusion, the decaffeination of coffee should be described since this is a process which is due shortly to go into commercial operation. In this process green coffee beans having a certain water content are treated with supercritical carbon dioxide. It seems obvious that CO_2 is physiologically unproblematic; nevertheless, we have carried out an experiment with radioactive CO_2 in order to show that during the destraction no substances are formed which remain in the coffee bean. No radioactivity could be detected in the destracted coffee. CO_2 can be regarded as the optimal solution for all problems which can arise in the conventional decaffeination with solvents. Of still greater interest seems to be the fact that the caffeine is selectively removed by the supercritical CO_2, *i. e.* no substances are lost which contribute to the aroma formed on roasting. Decaffeinated coffee and untreated coffee should then differ only in their pharmacological effect.

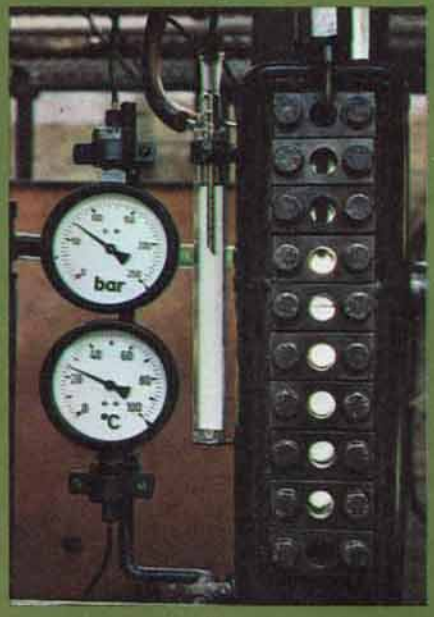
The decaffeination can be carried out in three ways (Fig. 7). In the first variation, presoaked green coffee beans are treated in a pressure vessel with CO_2 at 160—220 atm ($\rho \approx 0.4$—$0.65\,g\,cm^{-3}$), the CO_2 being continuously recycled (Fig. 7a). The caffeine diffuses out of the beans into the supercritical CO_2 and is then carried out of the pressure vessel into a washing tower where it is washed out with water at 70—90 °C. After 10 hours (at 90 °C) all of the caffeine is in the wash water which is then degassed and the caffeine recovered by distillation. The caffeine content in the bean is decreased



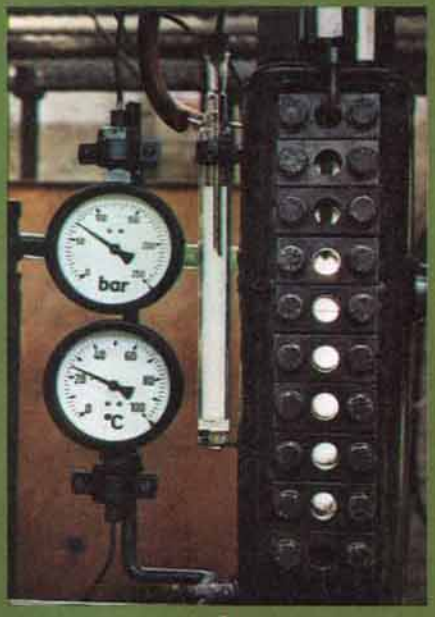
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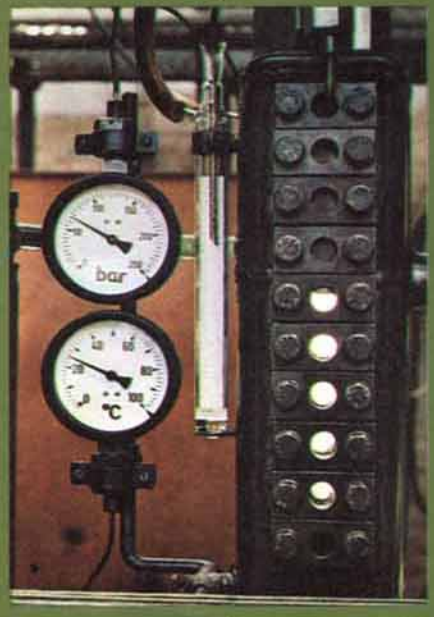
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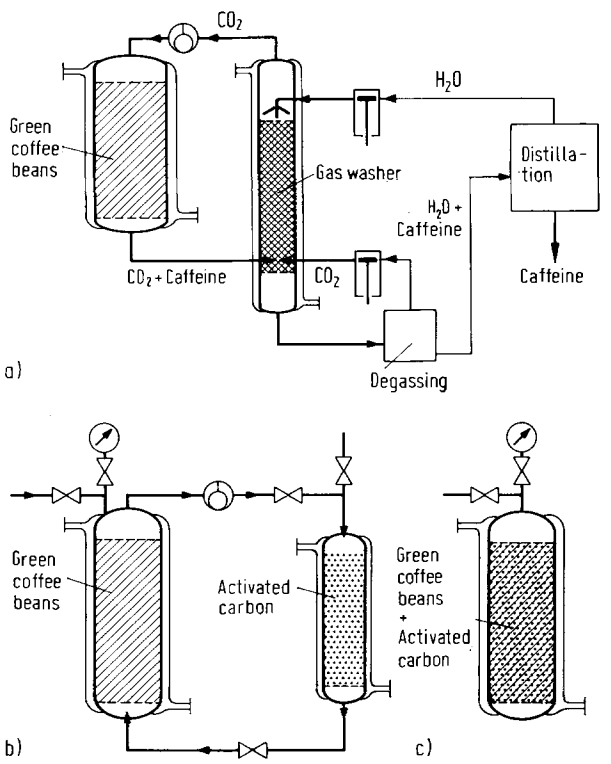


Fig. 7. Decaffeination of green coffee beans with supercritical CO_2. a) 70—90°C, 160—200 atm, $\rho \approx 0.4$—$0.65\,g\,cm^{-3}$. The caffeine is removed from the CO_2 by washing with water.
b) Same conditions as in a). The caffeine is removed from the CO_2 by adsorption on activated charcoal.
c) 90°C, 220 atm. The caffeine is removed from the CO_2, without recycling, by adsorption on activated charcoal admixed with the coffee beans.

from an initial value lying between 3 % and 0.7 % to a value as low as 0.02 %, *i.e.* lower than that stipulated (0.08 %). 3—5 l of wash water are needed to treat 1 kg of raw coffee.

The separation can be carried out with the help of active charcoal instead of water (Fig. 7b). However, in this case the caffeine must then be extracted from the charcoal.

A third variation (Fig. 7c) has certain advantages. The pressure vessel is charged with a mixture of coffee beans and active charcoal pellets whose diameter is such that they fill the space between the beans, *i.e.* the packing situation for the beans is practically identical to that in the absence of active charcoal. One kilogram of active charcoal is sufficient for 3 kg of coffee. A CO_2 pressure of 220 atm at 90°C is used. The caffeine in the supercritical CO_2 diffuses directly into the active charcoal without the need for recycling the gas. The required degree of decaffeination is reached after 5 hours. The mixture is then separated into its components by passing over a vibrating sieve.

The decaffeination of green coffee illustrates well the advantages associated with destraction and it can be anticipated that many other separation problems can be solved using this technique.

Figure caption to the color plate on facing page (Fig. 3) is on p. 704.

5. Summary

In conclusion let us summarize the most important characteristics of the destraction procedure:

1. Destraction is a pressure technique, necessarily requiring special investments.
2. High-boiling material can be separated with supercritical gases, whereby a loaded supercritical phase is formed. The method is particularly suitable for the isolation of thermally labile substances.
3. The ability of a supercritical gas phase to take up high-boiling material increases with increasing density or, at constant density, with increasing temperature.
4. The material taken up can be recovered by decreasing the density of the supercritical phase, either by reducing the pressure at constant temperature or by raising the temperature at constant pressure.
5. This effect can be used in fractionation.
6. In certain cases it is advantageous to carry out the extraction with liquid gas followed by a separation under supercritical conditions.
7. After separation of the destraction agent and destract, only recompression of the gas is needed. Solvent distillation as required in a conventional extraction is not necessary.
8. Substances belonging to the same chemical class are taken up into the supercritical phase in the order of their increasing boiling points (*e.g.* olefins in ethylene).
9. The separation according to boiling points can be overlapped by a separation according to the class of compound whereby the selective affinity to the supercritical gas is the controlling factor (*e.g.* caffeine in CO_2).

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Fluid Extraction of Hops, Spices, and Tobacco with Supercritical Gases[**]

By Peter Hubert and Otto G. Vitzthum[*]

This report provides an introduction to the principal methods of extraction with supercritical gases, illustrated by the processing of some natural products with carbon dioxide. The combination of pressure and temperature as process parameters makes it possible to vary the solvent power of the medium within certain ranges as desired without having to change the composition of the solvent, as would be necessary in conventional solvent extraction. The problem-free handling of carbon dioxide and also of the products obtained open up possibilities whose development has only just started.

1. Introduction

Extraction with organic solvents is a well-established method of selective separation of specific constituents from food and semi-luxury products. Extractants with a low boiling point such as ethyl acetate, methanol, dichloromethane, *etc.* are suitable on the one hand for isolating valuable constituents from such products as hops, spices, and oil seeds, and on the other hand for removing or reducing the level of less desirable accompanying substances (nicotine, caffeine). The extracts, such as those obtained from hops and spices, have a number of advantages over the starting material:

- the constituents are better utilized
- the products have a longer shelf-life
- greater uniformity is achieved because of the possibilities of standardization
- the products are sterile.

The solvents used for this purpose must meet the requirements of foodstuffs legislation, which can vary from country to country. The main requirements are as follows:

- a high degree of purity
- chemical stability
- considerable inertness, *i.e.* the extraction agent or traces of impurities present in it must not react chemically with the food constituents
- a low boiling point to facilitate removal of the solvent residue from the treated product
- freedom from toxic effects.

In recent years national and international bodies (Fremdstoffkommission der Deutschen Forschungsgemeinschaft; Food and Drug Administration (FDA), USA; EC Codex Committee; FAO/WHO, Geneva) have increasingly emphasized the importance of complying with such criteria.

2. Extraction with Supercritical Systems

2.1. Applications and Properties of Compressed Gases

The fact that compressed gases can dissolve solids was first demonstrated experimentally by *Hannay* and *Hogarth*[1] in 1879, who dissolved potassium iodide in supercritical ethanol and reprecipitated the salt by reducing the pressure.

Over the years there has been much discussion of the part played by the dissolving effects of supercritical gases in natural processes, for example the influence of methane in the production of crude oil[2] or the influence of water on rock formation in geological processes[3]. Only recently, however, has industrial exploitation of this phenomenon been proposed, for example for removing asphaltenes from crude oil[4], for the extraction of coal[5,6], and for the separation of mixtures of substances[7–11]. A number of authors have described the use of supercritical gases as carriers in supercritical fluid chromatography (SFC)[12–15] and also recently in combination with thin-layer chromatography[16]. In the early seventies advances were made in the solvent extraction of foods as a result of the introduction of separation with supercritical carbon dioxide. This meant that for the first time natural products such as coffee, tobacco, tea, cocoa, hops, spices, and oil seeds could be extracted without the use of organic solvents[17–26]. We shall not deal here in detail with the physicochemical principles of the solvent effects obtained with supercritical gases; for further information the reader is referred to relevant publications[9,27–36].

2.2. Methods of Processing Natural Products with Supercritical Carbon Dioxide

To assess the dissolving power of a supercritical gas it is necessary to determine the phase equilibria with the substances to be dissolved. However, on its own this does not provide sufficient information for estimating the extractability from vegetable material, since apart from the solubility the way in which the substance to be extracted is bound to the vegetable matrix has a considerable influence. For example, the strength of the binding of nicotine in raw tobacco varies: whereas some of it can be removed very easily by extraction, the rest is probably present as a complex salt with tobacco constituents such as chlorogenic acid, citric acid, *etc.* and is more difficult to extract.

For natural products that can be subjected to only moderate heating it is possible to use gases with appropriate critical temperatures, such as CO_2, as the extraction agents. This is generally the case when supercritical extraction can be carried out at about 10—80°C above T_c; 100°C above T_c should not be much exceeded. A selection of suitable gases has been given by *Stahl et al.*[16].

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[**] Based on a paper presented at the symposium "Extraction with Supercritical Gases", held at Essen on June 5, 1978.

Russian authors in particular have used liquid carbon dioxide to obtain extracts of natural products. The processing of tobacco has been described[37], as has the production of extracts from hops[38,39] and spices[40].

Extraction with supercritical in contrast to liquid CO_2 generally offers the following advantages: the substances to be extracted are much more soluble, and there is a wider range of possible operating temperatures. Density and dielectric constants can be changed by varying the pressure. Figure 1 shows how these two properties vary as a function of the pressure of carbon dioxide at 50 °C. It can be seen that the greatest changes take place between about 70 and 150 bar, and that both parameters increase only slightly above about 300 bar.

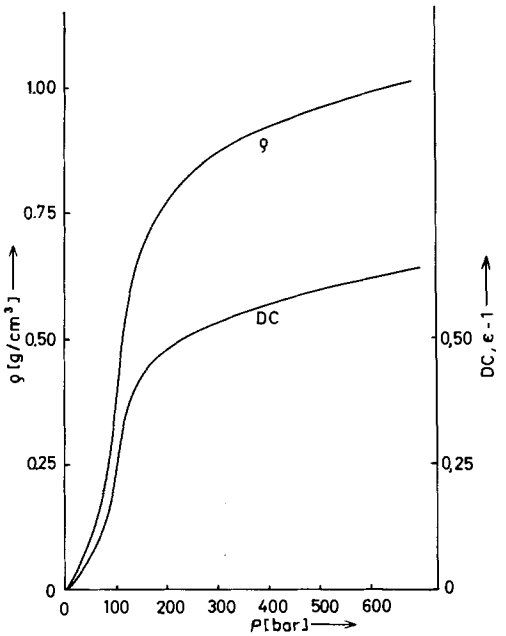


Fig. 1. Density and dielectric constant of CO_2 as a function of pressure (50 °C).

As the density increases, *i.e.* with increasing pressure, the solubility of less volatile components in the gas generally increases. According to our own measurements, the extraction rate, which also depends on the temperature-dependent diffusion of the constituents within the plant material, is at least 2.5 times as high with supercritical CO_2 as with liquid CO_2. The influence of the temperature can vary, depending on the pressure range. For example, Figure 2 shows that increasing the temperature at higher pressures results in an increased solubility of naphthalene in compressed ethylene, while at lower pressures such an increase in temperature reduces the solubility. Hence specific dissolution or separation effects can be achieved by selecting suitable combinations of pressure and temperature.

The method and apparatus used must be adapted to the raw material and to the purpose of the process. In one case the aim may be to obtain an extract and the remaining vegetable matrix or carrier substance may be either of no value (spices) or subjected to a further treatment with water (hops), while in another case it is the carrier substance that is wanted (tobacco) while the extracts are of secondary interest. The principle of extraction with supercritical gases is shown schematically in Figures 3 and 4 in the case of extract recovery and in Figure 5 in the case of recovery of the carrier substance.

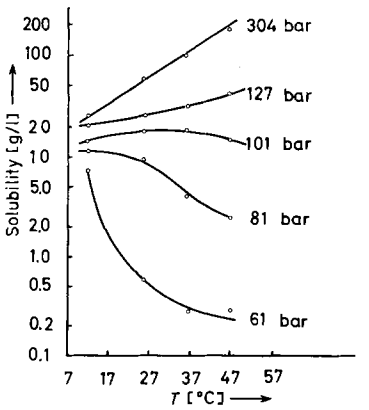


Fig. 2. Solubility of naphthalene in compressed ethylene as a function of temperature.

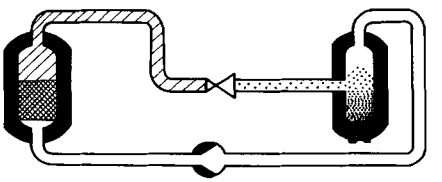


Fig. 3. High-pressure extraction with extract separation by variation of the pressure. Left, extraction stage; right, separation stage.

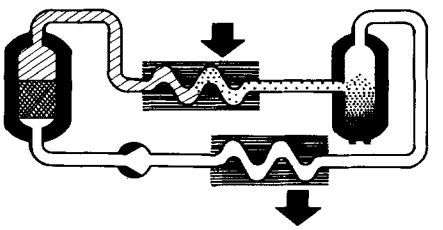


Fig. 4. High-pressure extraction with extract separation by variation of the temperature. Left, extraction stage; right, separation stage.

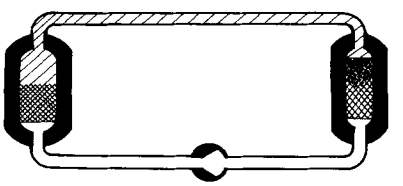


Fig. 5. High-pressure extraction with extract separation by adsorption. Left, extraction stage; right, adsorption.

In the extraction step the soluble constituents are solved by the compressed supercritical gas. The homogeneous phase, regarded as a solution, is decompressed as it passes through the throttle valve into the separation vessel (Fig. 3), with the result that the density of the gas decreases and the extract/solvent mixture separates into its component parts. The gas is then compressed again and returned to the extraction step. Separation can also be achieved by changing the temperature of the supercritical solution (Fig. 4). Figure 5 shows a process in which the dissolved extract is adsorbed onto suitable sorbents. This process, which can be run isobarically and isothermally in the whole circulation, is generally used when it is the carrier substance that is required (tobacco, tea, coffee).

2.3. Process Parameters in Extraction and Separation

Extraction pressures in the range of 80—300 bar are generally necessary to achieve adequate densities. This pressure range has so far been investigated most frequently. The occurrence of further dissolution phenomena at higher pressures cannot be excluded, but their use would probably be rejected for economic reasons. The preferred temperature range for extractions with CO_2 is about 35—80 °C.

There are several possible combinations of extraction and separation conditions that can be used to obtain hop and spice extracts[22, 23]. If we denote the extraction pressure by P_1 and the separation pressure by P_2, with corresponding temperatures T_1 and T_2, the different cases listed in Table 1 can be distinguished.

Table 1. Extraction with supercritical gases. Adjustment of the parameters for extraction (subscript 1) and separation (subscript 2).

Case 1:	$P_1 > P_c > P_2$ $T_1 > T_c > T_2$
Case 2:	$P_1 > P_c > P_2$ $T_1 \geqq T_2 > T_c$
Case 3:	$P_1 > P_2 > P_c$ $T_1 \geqq T_2 > T_c$
Case 4:	$P_1 = P_2 > P_c$ $T_1 \leqq T_2 > T_c$

In case 1 the supercritical gas phase is decompressed to a subcritical pressure and a subcritical temperature. Given these thermodynamic conditions, depending on P_1 and T_1 between 10 and 100% of liquid CO_2 will be found in the separation vessel together with the previously dissolved extract. Providing this extract is not also partly soluble in liquid CO_2, it will be deposited as a further phase. The CO_2 vapor in equilibrium with its liquid phase, and whose density is approximately 0.2 kg/l, has virtually no dissolving properties; to maintain the extraction circulation, it is drawn up by the feed pump, compressed again, and tempered. The method used in the case 1 means therefore that the liquid CO_2 in the separation vessel must be continuously evaporated, necessitating the supply of heat.

Since it is generally unnecessary to reduce the separation pressure and temperature to below their critical values in order to achieve separation (it is sufficient to adjust the density to a suitably low value), for practical purposes cases 2 and 3 are more realistic. Here P_2 is reduced either to below the critical pressure (case 2) or to a value between the extraction pressure and the critical pressure (case 3), while in both cases the separation temperatures are between the extraction temperature and the critical temperature. This also means that drier extracts are obtained. In general, if suitable pressure/temperature combinations are selected it is possible to achieve fractionation effects during the separation, using a multistage pressure cascade for example. Thus, it would appear to be possible in the case of pepper, for example, to obtain fractions enriched with essential oils or the hot flavor components. This also applies to hop extracts. However, it is also possible to achieve similar fractionation effects during the actual extraction with the aid of pressure/temperature programs. In case 4 the separation temperature depends on the pressure. Figure 2 illustrates the different effects of temperature on the solubility of naphthalene in ethylene. According to this, the temperature must be reduced when the pressure is high and raised when the pressure is low. Although case 4 would be of value because of the isobaric method of operation, it remains to be shown whether it is suitable for practical application, since the separation may not be as complete in this case as it is in cases 1—3 and the maximum thermal load that the extracts can withstand limits the rise of the temperature.

3. Properties of Carbon Dioxide as an Extraction Agent and Its Assessment from the Point of View of Food Regulations

The advantages of carbon dioxide, which is unobjectionable from the health point of view, over organic solvents make it appear an ideal extraction agent. It is ubiquitous in nature, *e.g.* in the air and mineral waters. It is what the plants breathe, and is produced when organic substances ferment. It is formed in many manufacturing processes in the food industry, *e.g.* in the production of beer and wine, in the baking of bread, *etc.*, and remains in these food products. Moreover, it is also used in artificially carbonating mineral waters. Being an "inert" gas, even in the supercritical state, CO_2 does not react in any way with the food constituents[41]. This is also the reason for its universal use for quick-freezing foods in the liquid and solid state. Even under the previous Federal German food legislation, CO_2 was not regarded as a foreign substance, and this classification has been retained in more recent legislation. Hence, together with air, nitrogen, and distilled or demineralized water, CO_2 is expressly excluded from the prohibition of additives. Table 2 suggests purity specifications for CO_2 used for extraction purposes.

Table 2. Specification for carbon dioxide for extraction purposes. Determination methods cf. [a—d].

Odor	neither burnt nor pungent	
Color	colorless	
CO_2 content	minimum 99.9 vol-%, measured in the liquid or gas phase	[a, b]
PH_3, H_2S and reducing organic substances	not detectable in 100 l (STP) of the gas	[a—c]
Foreign acids, *e.g.* SO_2, HCl	not detectable in 100 l (STP) of the gas	[a—c]
Carbon monoxide	<2 vol.-ppm	[c, d]
Oxidizable constituents	max. 1 vol.-ppm	[a]
Evaporation residue	max. 1 vol.-ppm	[a]

[a] *W. Fresenius, W. Schneider*, Mineralwasserzeitung *19*, No. 4 (1966).
[b] European Pharmacopeia, Vol. 2, pp. 175—177 (1971).
[c] Zusatzstoff-Verkehrs-VO, Anlage 2, Liste 8.
[d] Analysenmethoden HAG AG, Bremen. Vorschrift No. 081/2/01 (1976).

In addition to its solvent properties, CO_2 has the advantages of being neither flammable nor toxic, not maintaining combustion, and also not exerting a corrosive effect in combination with moisture on the materials used in processing natural products (stainless steel or plastics). It is also inexpensive and readily available in large quantities and high purity.

For all these reasons natural products have so far been processed predominantly with CO_2.

4. Production of Extracts with Supercritical Carbon Dioxide

4.1. Hop Processing

Hops have been used to make beer for some two thousand years. The use of hop extracts by the brewing industry is a more recent development, and is increasing in the interests of rationalization.

The valuable constituents of the hop resins are the soft resins which contain an α-acid fraction (mixture of several humulones) and a β-acid fraction (mixture of several lupulones). It is specifically the α-acids which, after isomerization in the brewing process, give beer its characteristic bitter taste. The structures of humulone and lupulone are shown in Figure 6.

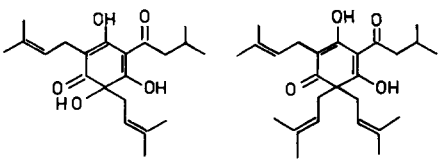


Fig. 6. Soft resin components of hops. Left, humulone; right, lupulone.

Conventional hop extraction generally employs dichloromethane, which has to be evaporated off after the resins have been extracted. The resulting extract is a pasty, dark-green to black-green mass, which is not permitted to contain more than 2.2 % solvent residue (CH_2Cl_2)[42].

To produce hop extract with supercritical CO_2 commercial hop pellets with a bulk density of approximately 0.65 kg/l were extracted under the conditions of case 3 (Table 1) without any further preparation. An olive-green, pasty extract with an intensive aroma of hops was obtained. The pellets had disintegrated into a powder, which was easily shaken out of the extraction vessel. Table 3 gives various analytical results.

Table 3. Hop analysis, CO_2 extraction.

	Pellets before CO_2 extraction	Pellets after CO_2 extraction	CO_2 extract	Degree of extraction	Extract, commercial
Water content [%]	6.0	5.4	7.0		8.0
Total resins [%]	30.3	4.3	90.0	89.9	88.5
Soft resins [%]	26.6	1.3	84.8	96.5	82.0
α-Acids [%]	12.6	0.2	41.2	98.9	39.5
β-Acids [%]	14.0	1.1	43.6	94.4	42.5
Hard resins [%]	3.7	3.0	5.2		6.5

It can be seen that the extent of extraction of the α-acids, almost 99 %, is above the required minimum of 95 %. The analyzed extract was obtained by single-stage pressure reduction (cf. Fig. 3). Extract separation by releasing the pressure in several stages is currently being investigated, this giving a choice of green or yellow extracts of different compositions.

4.2. Processing of Spices

The important constituents of spices are their aroma and flavor components. For industrial use, spices as such have a number of disadvantages, which, together with the trend toward rationalization in the food industry, have led to spice extracts or oleoresins being used. The advantages of these were mentioned in the introduction. The best extract or best oleoresin is a preparation that has aroma, flavor, hotness, *i. e.* all the organoleptic factors of the spice, and after dilution reconstitutes fully the organoleptic characteristics of the starting material[43]. The applications extend throughout the food industry. As there are so many spices, and the list of spice constituents[44] is steadily growing as a result of the refinement of analytical techniques, we shall not deal in detail with this subject. We shall consider only black pepper, nutmeg, and chilies, which can also be extracted with supercritical CO_2. Figure 7 shows the main constituent (98 %[43]) of the hot

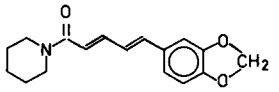


Fig. 7. Piperine, the main component of the hot principle of pepper.

principle of pepper, *i. e.* piperine. Other components are piperettine, piperoline A and B, and piperanine, which have similar structures.

The most important constituent of capsicum spices is a mixture of several amides, the capsaicine alkaloids, whose main components are capsaicine and dihydrocapsaicine[45] (Fig. 8).

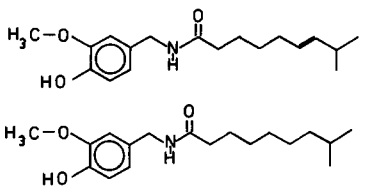


Fig. 8. Main components of the hot principle of capsicum. Top, capsaicine; bottom, dihydrocapsaicine.

The results of spice extraction with supercritical CO_2 are described for pepper, nutmeg, and chilies. A few analytical results are compared in Table 4 with values for the commercial extracts.

Table 4. Spice analysis, CO_2 extraction.

	Material before CO_2 extraction	Material after CO_2 extraction	CO_2 extracted	Degree of extraction	Extract, commercial (usually CH_2Cl_2)
	Pepper				
Piperine [%]	10.1	0.3	44.0	97.7	41.2
Essential oil [%]	3.5	<0.1	12.7	81.1	15.0
Water [%]	9.3	6.2	7.0		0.2
Color of extract			yellow		olive green
	Nutmeg				
Essential oil [%]	7.4	<0.1	19.0	99.0	20.0
Hexane-soluble matter [%]	46.0	1.7	100	98.0	100
Water [%]	4.9	4.4	1.6		0.1
Color of extract			whitish yellow		yellowish-brown
	Chilies				
Capsaicine [%]	0.86	0.03	4.9	97.0	4.7
Water [%]	3.2	1.8	1.3		0.1
Color of extract			red		red

Ground black pepper was extracted under the conditions of case 1 (Table 1). The extract obtained was yellow and pasty and had a very strong smell of pepper. The degree of extraction of piperine was almost 98 %, *i. e.* above the minimum required yield of 95 %, and the piperine content of the extract (44 %) was roughly the same as that of the commercial product (Table 4). The extraction of ground nutmegs under the conditions of case 3 yielded a pale yellow nutmeg butter with a pronounced nutmeg aroma. The degree of extraction was 98 %. The extraction of ground chilies under the conditions of case 1 gave a red oil, the degree of extraction, calculated for capsaicine, being 97 %.

5. Obtaining the Carrier Material: Processing of Tobacco with Supercritical Carbon Dioxide

The greater part of tobacco produced nowadays goes into cigarettes, and the trend toward mild tobacco has risen steadily over the last twenty years. The term "mild" is used here in particular to describe a material whose smoke contains relatively little nicotine and condensate when it is burnt. Tobaccos of this type with a good aroma and a low nicotine content are not available in unlimited quantities, and because of the concern about damage to health that may be caused by nicotine, attempts have already been made to remove this constituent from tobacco[46–51]. Since tobacco treated with organic solvents, for example, often acquires a rubbery structure, special processes have been suggested to avoid this effect, which is extremely disadvantageous to further processing.

In the meantime interest has also grown in other potentially harmful substances such as may appear in smoke condensates.

The primary aim of processing raw tobacco with supercritical CO_2 is to reduce the nicotine content to the desired levels with the minimum loss of aroma. This was found to have the side effect of a certain expansion of the tobacco. It is also possible to obtain a raw tobacco aroma equivalent to that obtained with the method described for extract separation, to transfer aroma from one tobacco to another, or even to impregnate a neutral matrix with the tobacco aroma.

5.1. Preparation of the Material for Extraction

In principle raw tobacco in any form can be used, including leaf ribs and tobacco dust. Apart from conditioning (moistening or drying), the tobacco requires no further preparation. The additives commonly used in tobacco preparation, such as moisture-retainers, sauces, flavors, binders, *etc.* are not added until the tobacco has been treated by the described method.

5.2. Single-Stage and Multistage Processing

The presence of water is essential in the extraction of nicotine. However, at the normal moisture content of tobacco (*ca.* 10—13 %), supercritical CO_2 extracts insufficient nicotine, or none at all, but removes the aroma instead. It should nevertheless be mentioned at this point that tobaccos of different origins behave very differently (Fig. 9), this also applying in all other stages of the process.

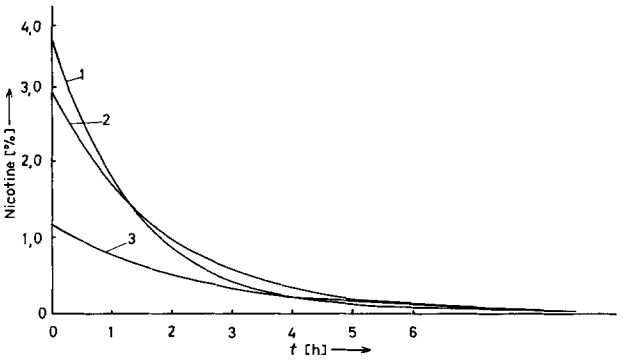


Fig. 9. Residual nicotine content as a function of processing time for three tobaccos of different origins: 1, Burley; 2, Virginia; 3, Orient.

In the single-stage process the moisture content of the tobacco is increased up to 25 %, in special cases even higher, and a stream of supercritical gas is passed through the material. The pressures are approximately 300 bar, and the temperatures are between the T_c of the gas and about 100 °C. The dissolved nicotine is separated by reducing the pressure or by changing the temperature (cf. Section 2.2) or is bound by adsorption onto suitable sorbents[18]. After drying the tobacco is immediately ready for further processing. A multistage process[19] may prove suitable for tobaccos for which the single-stage method has a detrimental effect on aroma. Figure 10 shows a block diagram of a three-stage process as a section of a continuous production process.

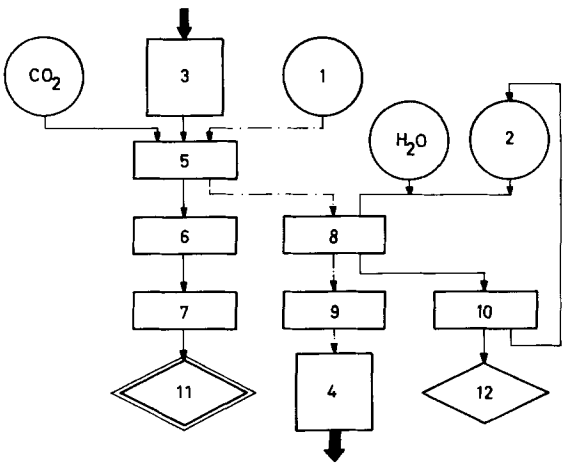


Fig. 10. Multistage extraction of nicotine from tobacco with supercritical CO_2. 1, Tobacco (starting material); 2, nicotine adsorbent; 3, nicotine-reduced tobacco from preceding cycle; 4, nicotine-reduced tobacco produced from 1 in the process shown for the next cycle; 5, transfer of aroma from 1 to 3; 6, aroma distribution; 7, conditioning; 8, removal of nicotine from the (dearomatized) batch produced from 1 with supercritical CO_2; 9, drying; 10, regeneration of the adsorbent; 11, nicotine-reduced, re-aromatized tobacco (finished product); 12, nicotine (by-product).

The arrow at the top indicates the intake of a previously denicotinized batch, the arrow at the bottom discharge of the nicotine-reduced batch produced in the section shown to the next cycle. In the first stage the aroma is removed from the fresh material. (As a rule, less nicotine will be extracted the drier the tobacco.) The aroma could be isolated as an extract in the same way as described for hop and spice extraction. In the present case, the aroma is used to impregnate a previously denicotinized batch, *i. e.* the aroma-carrying gas stream is allowed to expand in the nicotine-reduced batch.

The de-aromatized tobacco is moistened for the second stage and the nicotine is then removed in an isobaric and isothermal recycling operation. Selective sorbents are used for the nicotine. Regeneration of these sorbents affords nicotine as a by-product. The third stage of the process involves a homogeneous distribution of the transferred aroma in the bulk by repeated dissolution and reprecipitation. The rearomatized tobacco can then, after conditioning if necessary, be used directly for further processing.

5.3. Quality Characteristics of the Treated Tobacco

When the treated tobacco is discharged from the extraction vessel, a certain expansion of its fibers is observed as a result of the removal of gas residue from the vegetable tissue. This effect is dependent on the moisture content, the temperature, and several other parameters and can be controlled within certain limits. The external appearance of the product remains unchanged or may change only slightly to a lighter or darker color, this again depending on the origin and the treatment process. Table 5 shows the results of analysis of smoke from

Table 5. Results of smoke analysis performed on cigarettes made from untreated tobacco and tobacco treated by the three-stage process.

		Untreated tobacco	Treated tobacco
Length of cigarette	[mm]	84.0	84.0
Length of filter	[mm]	20.0	20.0
Length of total stub	[mm]	28.0	28.0
Diameter	[mm]	8.03	8.06
Effective sample weight	[mg]	1126	1070
Cigarette paper	[mg]	46	42
Filter and wrapping	[mg]	162	162
Quantity of burnt tobacco	[mg]	803	758
Air-flow resistance of cigarette	[torr]	8.5	8.6
Air-flow resistance of filter	[torr]	4.7	4.7
Air permeability of cigarette paper	[(l/h)]	99.6	100.0
Moisture content of cigarette	[%]	12.4	12.5
Nicotine content of tobacco	[%]	1.52	0.08
Number of draws		9.9	8.5
Nicotine content of smoke	[mg]	1.08	0.06
Nicotine in main smoke	[mg/g]	1.34	0.07

cigarettes made from untreated tobacco and from tobacco treated by the three-stage process. The nicotine content of the tobacco is reduced by 94.7 % and that of the main smoke

Table 6. Analysis of raw tobacco in various stages of processing, CO_2 extraction (nicotine contents in the dry substance).

	Tobacco 1 [%]	Tobacco 2 [%]
Starting material	2.47	1.05
after removal of the aroma	2.33	1.00
after reduction of nicotine	0.09	0.04
after re-aromatizing	0.16	0.08

by 94.8 %. Table 6 compares the nicotine contents of two tobaccos at intermediate stages of the multistage process.

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Physicochemical Principles of Extraction with Supercritical Gases[**]

By Gerhard M. Schneider[*]

The present review considers some physicochemical properties of fluid mixtures that are of importance for fluid extraction and supercritical fluid chromatography (SFC). Firstly, the important types of phase diagrams are treated, the occurrence of solid phases also being considered in some simple cases. Specific examples are given of mixtures of a highly volatile component I (*e.g.* CO_2, C_2H_6) with a relatively involatile component II (*e.g.* squalane) of very different molecular size, shape, structure, and/or polarity, and it is shown how the rather complicated types of phase diagrams can be calculated and correlated. The importance of fluid mixtures extends far beyond the fields of science and technology reviewed.

1. Introduction

As shown in other papers presented at the Symposium "Extraction with Supercritical Gases", fluid extraction and supercritical fluid chromatography (SFC) have already found interesting and important applications. This review considers some physicochemical properties of fluid mixtures pertaining to these new methods of separation; the main emphasis will be placed on phase equilibria and transport properties.

2. Phase Equilibria of Fluid Mixtures

Fluid mixtures may exhibit very different and complicated types of phase behavior. The historical development and present knowledge in this field have been described in several books[1-3] and review articles[4-7] giving extensive references to the relevant literature. This article is concerned mainly with recent publications, which also provide access to less recent work.

Our discussion of the phase-theoretical principles will start from the well-known phase diagram of carbon dioxide, which is still by far the most important solvent in fluid extraction. The situation encountered here and with the fluid mixtures discussed below is also typical for other supercritical extractants such as ethane, ethylene, N_2O, *etc.*

2.1. Phase Diagram of Pure Carbon Dioxide

Figure 1 shows the $p(T)$ phase diagram of pure carbon dioxide: s is a solid, l a liquid, and g a gaseous phase. Curves where two phases coexist are dotted. The vapor pressure curve lg starts at the triple point Tr [$T_{tr}=(216.58\pm0.01)$ K, $p_{tr}=(5.185\pm0.005)$ bar[8]] and ends at the critical point CP [$T_c=(304.20\pm0.05)$ K, $p_c=(73.858\pm0.05)$ bar, $\rho_c=(0.468\pm0.005)$ g·cm^{-3}[8]]. The melting pressure curve ls starts at the triple point and rises steeply with increasing temperatures and pressures [$(dT/dp)^{ls}_{tr}=46.55$ bar·K^{-1}[8]]; a temperature of 40°C on the melting pressure curve is reached at about 7 kbar. The sublimation pressure curve gs is of no significance for the present problems.

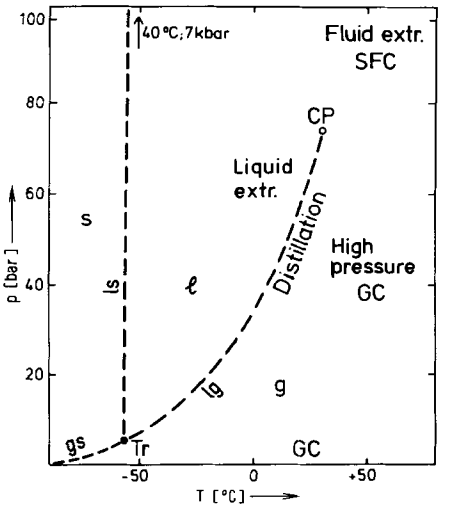


Fig. 1. $p(T)$ phase diagram of pure carbon dioxide [g = gas, l = liquid, s = solid; CP = critical point (here lg), Tr = triple point (here gls)].

In Figure 1 the approximate ranges are additionally marked where separation processes can be effected. Distillation will normally be possible near the vapor pressure curve lg. For liquid extraction the liquid range l must be reached. In gas chromatography (GC) carbon dioxide is used as a mobile phase in the gaseous region g at temperatures above ambient and at pressures up to some 10^1 bar. Fluid extraction and supercritical fluid chromatography, however, are limited to the supercritical region above T_c and p_c.

2.2. Phase Behavior of Fluid Binary Systems

In the following, the principal types of phase behavior will be discussed that may be encountered with mixtures of CO_2 or similar gases mainly with organic substances. Recent phase theoretical investigations have shown that the different types can be easily classified according to the shape of their critical curves[1,5-7]. The following discussion also follows this approach (see[9]).

Figure 2a shows the pTx surface for the liquid-gas phase equilibria of a binary system in the simplest case. The dotted lines are the vapor pressure curves of the pure components I and II respectively; here and in the following diagrams

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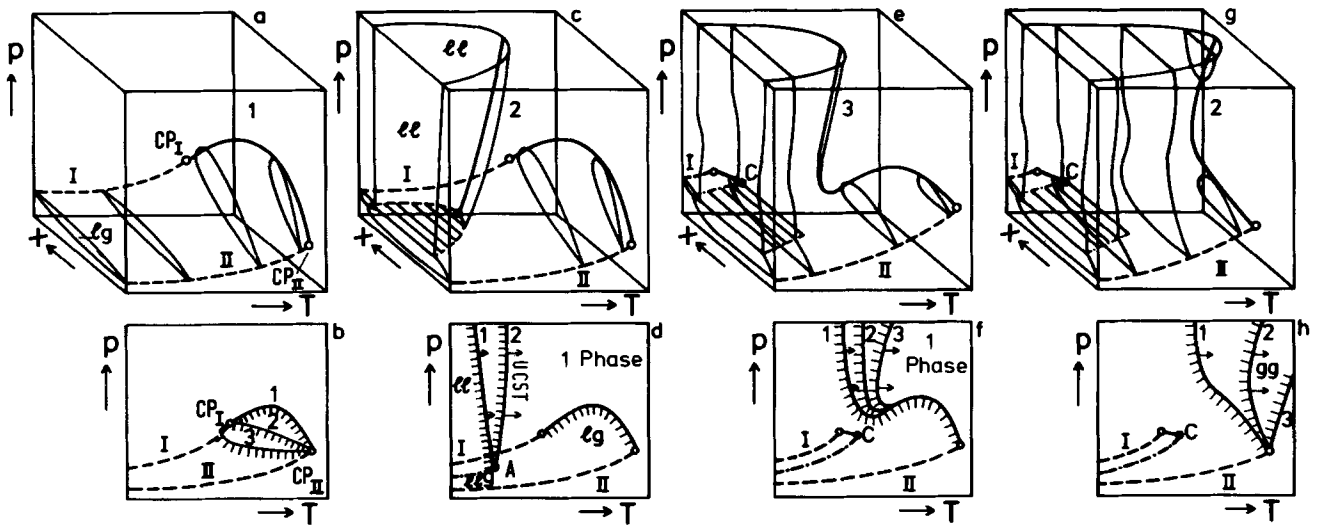


Fig. 2. Fluid phase equilibria in binary systems: pTx surfaces (a, c, e, g) and $p(T)$ projections ("$p(T)$ diagrams") (b, d, f, h) (schematic; for details and examples see text): ——— = vapor pressure curve of pure component; ——— = critical curve, ——— = $p(x)$ isotherm, –·–·– = three-phase line llg, UCST = upper critical solution temperature, A, C = critical endpoint). x = mole fraction = $n_I/(n_I + n_{II}) = 1 - n_{II}/(n_I + n_{II})$.

component I corresponds to carbon dioxide or a similar highly volatile substance, and component II is an organic compound. The vapor pressure curves end at the critical points CP_I and CP_{II} of the pure components I and II respectively. Some binary $p(x)$ isotherms are also schematically presented. For $T < T_c(CO_2)$ they have the well-known spindle-like shape. Homogeneous liquid states occur above, and homogeneous gaseous states below each $p(x)$ isotherm. Coexisting phases are connected by an horizontal line, called a connode. For $T > T_c(CO_2)$, the $p(x)$ isotherms no longer run to the side of pure component I but form characteristic loops. At the maximum of each isothermal $p(x)$ loop the connode degenerates to a point, the critical point CP of the $p(x)$ section at the given temperature; here the liquid and gaseous phases become identical. The curve that connects the critical points of all isotherms is the binary critical curve. The types and shapes of different sections through the pTx surface (*e.g.* of $T(x)$ isobars or of $p(T)$ curves for x = const (called isopleths)) are discussed in the literature (*e.g.* [10, 11]). Numerous examples are presented by *Hicks* and *Young* [12].

Type 1 in Figure 2b corresponds to the $p(T)$ projection of the schematic three-dimensional phase diagram in Figure 2a; such a projection is usually called a $p(T)$ diagram of the binary system considered. For type 2 the critical curve is monotonous between CP_I and CP_{II}, and type 3 exhibits a temperature minimum on the critical line. Here, as well as in the following figures, heterogeneous regions are marked by hatching. At conditions of temperature and pressure beyond the critical line the components are miscible in all proportions. For fluid extraction this means that, beyond this curve, substances can be dissolved completely in the supercritical solvent whereas for reprecipitation heterogeneous regions have to be entered.

In Figures 2c and 2d, separation into two liquid phases is also considered. For the types given the critical curve lg is not interrupted and runs through the usual pressure maximum. At temperatures far below the critical temperature of pure component I, liquid-liquid immiscibility is also found. The branch of the critical curve ll that starts at the critical endpoint A corresponds to upper critical solution temperatures (UCST) that may rise slightly with increasing pressure (type 2, for details see Figure 4) or decline (type 1).

The lower the mutual miscibility of components I and II the more the branch ll of the critical curve that has to be attributed to liquid-liquid equilibria will be shifted to higher temperatures. It can eventually penetrate the temperature and pressure range of the critical phenomena liquid-gas and merge continuously with the critical curve lg such as shown in Figure 2e and 2f. Here the branch of the critical curve at high pressures can exhibit different shapes: It may run to lower temperatures and higher pressures (type 1 in Figure 2f), or (within the limits of experimental error) vertically to higher pressures (type 2 in Figure 2f), or it can bend back again and assume a positive slope at high pressures (type 3 in Figure 2f); this type is represented three-dimensionally in Figure 2e (for details see Figure 5).

For further decreasing mutual miscibility of the components critical $p(T)$ curves without any pressure maximum or minimum as in Figures 2g and 2h will be obtained. Here the branch starting at CP_{II} can exhibit different shapes:

1) It may start from CP_{II} with a negative slope and become steeper and steeper with increasing pressure without reaching, however, any temperature minimum within the experimental range (type 1 in Figure 2h), or
2) it may run through a temperature minimum (type 2 in Figure 2h, three-dimensionally represented in Figure 2g; gas-gas equilibrium of the 2nd kind), or
3) it may start from CP_{II} with a positive slope and proceed directly to increasing temperatures and pressures (type 3 in Figure 2h; gas-gas equilibrium of the 1st kind).

Two important modifications of the phase behavior as shown in Figures 2c—h are discussed in Figure 3. In Figures 3a and 3b the branch of the critical curve that starts from the critical endpoint A on the three-phase line llg has to be attributed to upper critical solution temperatures (UCST) for liquid-liquid equilibria whereas that starting from B first corresponds to lower critical solution temperatures (LCST) and then merges continuously into the critical curve lg. With

increasing mutual miscibility (*e.g.* for smaller differences of components I and II in size, shape, and/or polarity) the branch starting at A is shifted to lower temperatures and may disappear completely below the crystallization surface, whereas on the branch starting from B the liquid-liquid critical phenomena will disappear until finally a phase diagram of the simple type 2a or 2b results. With *decreasing* mutual miscibility in comparison with Figures 3a and 3b types 3, 2′, 2, 1′, and 1 in Figure 3d will be successively obtained that resemble the corresponding types in Figures 2e through 2h.

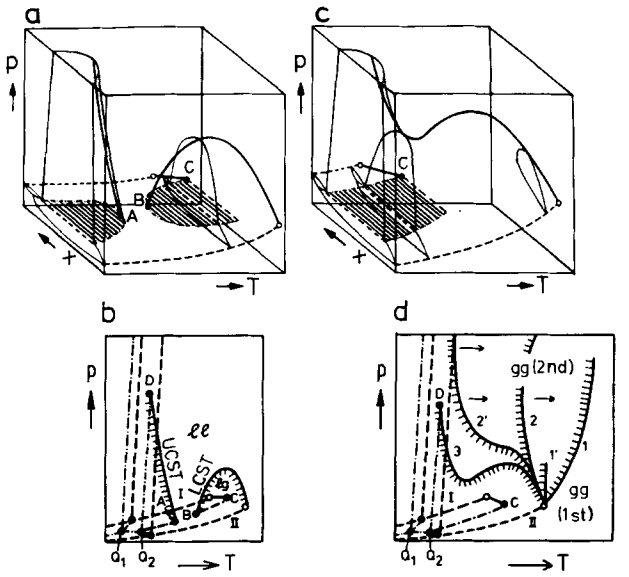


Fig. 3. Fluid phase equilibria in binary systems: Supplements to Figure 2 (schematic; for details and examples see text; for symbols see Figure 2; A, B, C, D = critical endpoint; Q = quadruple point; LCST = lower critical solution temperature).

Figures 2 and 3 show that for fluid binary mixtures of components differing more and more in size, shape, structure, and/or polarity a whole pattern of different types of phase behavior and critical curves has to be considered. They also demonstrate that there are continuous transitions between liquid-gas, liquid-liquid, and gas-gas equilibria. For a detailed discussion and many examples see [1, 3–7, 9, 10–12].

2.3. Detailed Treatment of Types of Diagram of Significance for Fluid Extraction

Figure 4a shows the schematic $p(T)$ diagram of a binary system according to Figure 2c on a larger scale (= type 2 in Fig. 2d). This type is found for mixtures of CO_2 with octane, decane, or dodecane[7, 13] as well as with 2-hexanol or 2-octanol[9] (see Figures 11 and 12). The branch of the critical curve lying between CP_I and CP_{II} corresponds to liquid-gas (lg) critical phenomena whereas the branch ll starting from A has to be attributed to upper critical solution temperatures for liquid-liquid equilibria as a function of pressure. Some characteristic $p(x)$ isotherms are schematically represented in Figures 4b—4d.

In the homogeneous region beyond the critical curves the substances I and II are completely miscible in all proportions, *e.g.* at point G in Figure 4a. Under these conditions low-volatile substances can be completely dissolved by the supercritical

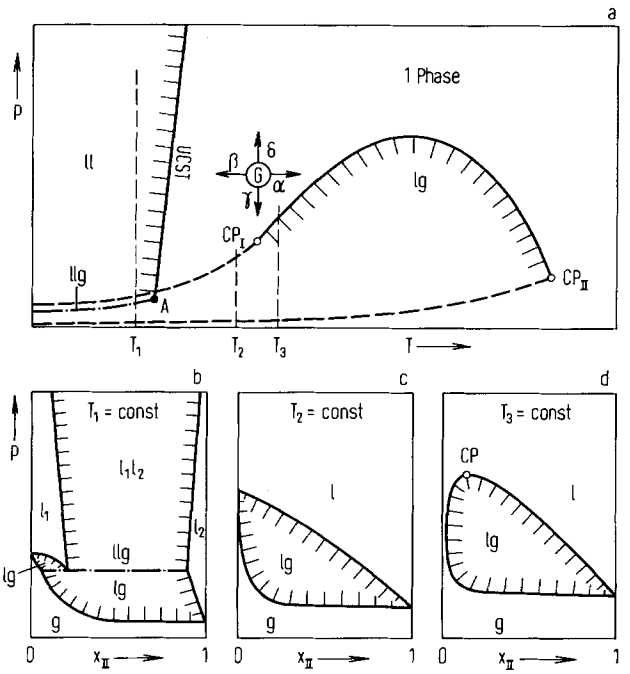


Fig. 4. $p(T)$ diagram (a) and selected $p(x)$ isotherms (b—d) for binary systems of the type CO_2 + octane, CO_2 + decane, CO_2 + dodecane, CO_2 + 2-octanol (schematic; see text; for symbols see Figures 2 and 3).

highly compressed gas I. Here reprecipitation (*e.g.* for the separation of the dissolved substance from the extractant) is possible by a temperature increase (case α), by a (usually large) temperature decrease (case β), by a pressure decrease (case γ) and (exceptionally) by a (usually pronounced) pressure increase (case δ). Moreover, for precipitation the types shown in Figures 2 and 3 differ characteristically: Phase separation with decreasing pressure at constant temperature is possible in all cases except for type 3 in Figure 2h and type 1 in Figure 3d whereas separation with increasing temperature at constant pressure is limited to suitable regions of the types 2a—f, 3a—c and type 3 in Figure 3d.

Figure 5a shows the schematic $p(T)$ phase diagram of a binary system according to Figure 2e on a larger scale; this type is found for CO_2 + hexadecane[13] (Figures 11 and 12) and CO_2 + 2,6,10,15,19,23-hexamethyltetracosane (squalane)[14] (see Figures 8, 11, 12, 14). Precipitation (*e.g.* starting from point G in Figure 5a) is again possible with increasing temperature (case α), decreasing temperature (case β), decreasing pressure (case γ), and (strongly) increasing pressure (case δ).

Some characteristic isothermal $p(x)$ sections for $T > T_{c(I)}$ are shown in Figures 5b—5d. For the isotherm at $T = \text{const} = T_1$ in Figure 5b the two-phase region at pressures below the three-phase line llg corresponds to liquid-gas equilibria; here the branch a on the right represents the solubility of the supercritical component I in the liquid component II and the branch b on the left that of the liquid component II in the supercritical component I. At pressures above the three-phase line the two-phase liquid-gas region occurring at high contents of component I vanishes at the binary critical point CP; additionally a liquid-liquid miscibility gap ll is found. The isotherm corresponding to Figure 5c is situated at such a high temperature T_2 that the three-phase line llg is no

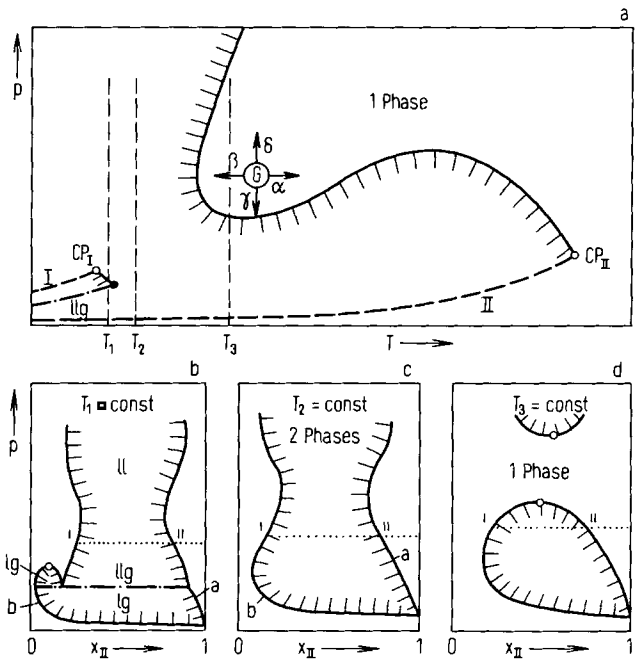


Fig. 5. $p(T)$ diagram (a) and selected $p(x)$ isotherms (b—d) for binary systems of the type CO_2 + hexadecane, CO_2 + squalane, CO_2 + 2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaene (squalene) (schematic; see text; for symbols see Figures 2 and 3).

longer cut and liquid-liquid and liquid-gas equilibria can no longer be distinguished. The isotherm in Figure 5d consists of two completely separated two-phase regions.

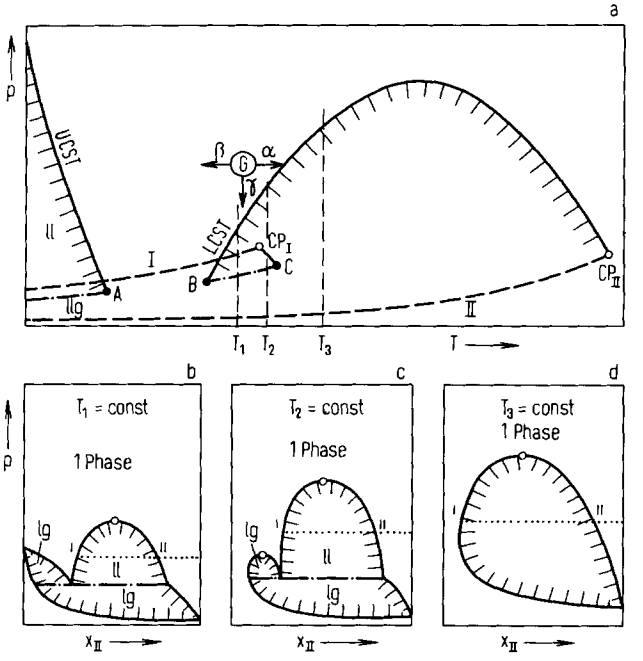


Fig. 6. $p(T)$ diagram (a) and selected $p(x)$ isotherms (b—d) for binary systems of the type CO_2 + nitrobenzene, C_2H_6 + squalane (schematic; see text; for symbols see Figures 2 and 3).

Figure 6 shows the schematic $p(T)$ diagram of binary systems according to Figures 3a and 3b with upper (UCST) and lower (LCST) critical solution temperatures. This type is found for binary mixtures of CO_2 with nitrobenzene, 2-nitrophenol, or 1,4-dichlorobenzene, of C_2H_6 with squalane (see Figure 14) or 1,3,5-trichlorobenzene, of CH_4 with 1-hexene or 3,3-dimethylpentane, as well as for solutions of polymers or oligomers in low-molecular solvents[1, 7]. Precipitation (*e.g.* starting from point G in Figure 6a) is possible with increasing (case α) or decreasing (case β) temperature and decreasing pressure (case γ). Some characteristic $p(x)$ isotherms are represented in Figures 6b—6d. As in Figure 5b the two-phase regions in Figures 6b and 6c below and above the three-phase line correspond to liquid-gas and liquid-liquid equilibria respectively. For the $p(x)$ isotherm at $T = \text{const} = T_3$ in Figure 6d liquid-gas and liquid-liquid equilibria are no longer distinguishable.

For the discussion of problems in fluid extraction and SFC $p(c)$ isotherms (where c = concentration, *e.g.* in $g \cdot cm^{-3}$) would be more suitable than $p(x)$ isotherms such as given in Figures 4b—4d, 5b—5d, 6b—6d, 7b, 7d, and 7e. Since hardly any pVT data for coexisting phases are available, the calculation of concentrations is impossible in most cases and thus $p(c)$ isotherms are known for a few systems of interest only (such as in Figures 9b, 9c, and 10).

According to Figures 4, 5, and 6 unusual $T(x)$ isobars and consequently an extraordinary temperature dependence of solubilities at constant pressure have to be expected, *e.g.* for systems of the type 5a a maximum solubility should be found with increasing temperature at low pressures (say below the pressure minimum of the critical curve) whereas at much higher pressures only a solubility increase with rising temperature should be possible. Such a temperature dependence is already known, *e.g.*, for the solubility of naphthalene in supercritical ethylene[76].

The solubility phenomena described by *Zosel*[15] can qualitatively be explained from Figures 5b and 5c or 6b and 6c. For a constant pressure above the three-phase line, CO_2 is first dissolved in the liquid under test until the mole fraction x_2'' is reached. With further addition of CO_2 phase separation into two phases with the mole fractions x_2' and x_2'' is found, phase ′ being taken from the high pressure vessel until all phase ″ is transformed into phase ′. For the types in Figures 5b, 6b, and 6c the three-phase line llg is reached with decreasing pressure and gas bubbles such as mentioned by *Zosel* appear; for the types in Figures 5c, 5d, and 6d, however, (transient) turbidity is observed because of additional phase separation along the equilibrium curves, the latter runs being effected in the ranges of temperature and pressure recommended for fluid extraction by *Zosel. Zhuze et al.*[16] have probably been concerned mainly with diagrams according to Figures 5b, 6b, and 6c that will also correspond to the well-known process for production of bitumen from petroleum residues by selective precipitation with propane.

2.4. Occurrence of Solid Phases

Up to now mixtures have been considered that consist of fluid phases only. For fluid extraction, the dissolution of solid substances by a supercritical fluid phase, however, is of considerable importance, *e.g.* for most of the separations described by *Stahl*[17].

The phase relationships are schematically represented in Figure 7 for a case where the critical fluid phase behavior corresponds to the simple type of Figure 2a. For the solid phases complete immiscibility of the components is assumed. In Figure 7a the triple point temperature $T_{tr(II)}$ of pure com-

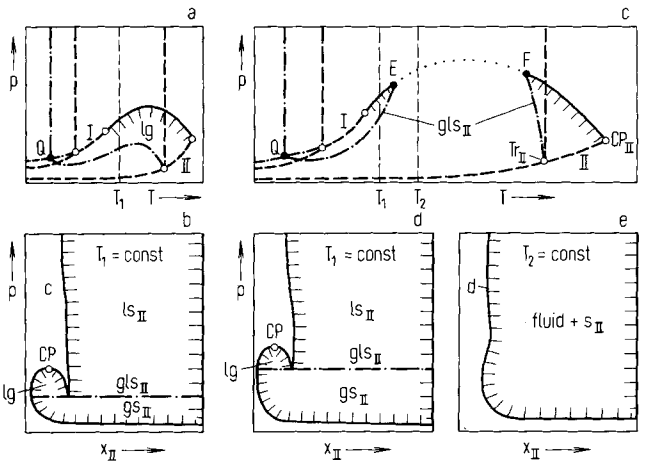


Fig. 7. $p(T)$ diagram (a; c) and selected $p(x)$ isotherms (b; d and e) for binary systems with occurrence of solid phases in the supercritical region lg in simple cases (schematically; see text; for symbols see Fig. 2).

ponent II (here the organic substance to be extracted) is higher than the critical temperature $T_{c(I)}$ of pure component I (here the supercritical solvent, *e.g.* CO_2). In Figure 7b a typical $p(x)$ isotherm slightly above $T_{c(I)}$ is shown. For pressures above the three-phase line gls_{II} the solubility of solid II in the fluid phase is given by curve c (*e.g.* C_2H_6 + 1,4-dichlorobenzene).

In Figure 7c the three-phase line gls_{II} runs to pressures high enough for it to cut the critical line lg twice at the critical endpoints E and F. Figures 7d and 7e show two characteristic $p(x)$ isotherms. Whereas the diagrams 7b and 7d are very similar, the three-phase line gls_{II} is no longer cut in Figure 7e and the solubility of solid component II in the fluid phase is given by curve d. Examples for the latter type are CO_2 + diphenylamine, C_2H_6 + naphthalene, CH_4 + naphthalene, binary mixtures of C_2H_4 with diphenyl, naphthalene, anthracene, hexachloroethane, *etc.* (for references, see [18]) as well as $H_2O + SiO_2$ [19]. It will probably occur rather often in the systems investigated by *Stahl*[17].

A more complicated critical behavior in the fluid phase (*e.g.*, as in Figures 2c—2h) can also be considered. The most important types have been discussed by *Zernike*[10], *Rowlinson*[1], and *Schneider*[7] and two types of interest for fluid extraction are represented in the $p(T)$ diagrams given in Figures 3b (*e.g.*, CH_4 + 1-hexene) and 3d (*e.g.*, CH_4 + methylcyclopentane) (for references and details, see [7]). Similar diagrams are also important for the solubility of inorganic compounds in supercritical water (see *Franck*[20], *Horvath*[21]).

2.5. Ternary Systems

For the simultaneous extraction of two components A and B with CO_2 the phase diagram of the ternary system A + B + CO_2 is of interest, especially when the concentrations of A and B are relatively high. Extensive data exist for $T < T_c(CO_2)$ [38]. From the sparse experimental material available for $T > T_c(CO_2)$, only measurements on the ternary systems CO_2 + heptane + methanol[39], $CO_2 + H_2O$ + acetic acid[39], $CO_2 + H_2O$ + acetone[39], CO_2 + acetone + glycerides[40], CO_2 + *n*-butylbenzene + 2-methylnaphthalene[74] will be mentioned here. Additional data exist for other supercritical solvents, *e.g.* C_2H_4 + quinoline + 2,4-xylenol, C_2H_4 + quinoline + dodecane[73] (for references to earlier work, see [40,74]).

3. Data for Selected Systems

3.1. Experimental Procedure

Two principal methods are used for determination of fluid phase equilibria at high pressure.

1) The analytical method:

The temperature, pressure, and concentration in the heterogeneous region are set at chosen values and the compositions of the coexisting phases are determined (mostly for an aliquot sample). The method is generally difficult and tedious, but multicomponent systems can also be investigated.

2) The synthetic method:

The autoclave is filled with a mixture of known composition in the homogeneous region. The temperature and/or pressure are then varied until a second phase appears. Thus parts of $p(T)$ curves for x = const ("isopleths")—or in rare cases the whole curve—can be determined. Phase separation is mostly detected visually but other methods can also be used[22, 75]. Normally this method is quick and simple and simultaneous pVT measurements are possible; for systems with more than two components, however, the connodes cannot be determined.

These and other methods are discussed in detail in recent review articles by *Schneider*[22] and *Young*[23] where many references are given and where the most important experimental set-ups from the literature are described.

3.2. Discussion of Selected Systems

Figures 8a and 8b give data for the system CO_2 + squalane that have been determined in a simple apparatus by *Liphard*[14] according to the synthetic method. This substance is well-suited for a phase-theoretical discussion of the foundations of fluid-extraction. Squalane is an alkane which is liquid at room temperature and has a relatively high molecular mass; it is synthesized by hydrogenation of the natural product squalene and being a well-known stationary phase in GC it is readily available. Figure 8a shows some isopleths between 6.9 and 72.8 wt % $C_{30}H_{62}$ and Figure 8b some pressure (composition) isotherms that have been interpolated from the isopleths in Figure 8a; the upper and lower abscissa show the mole fraction x and the content of the hydrocarbon in wt % respectively. The type of phase behavior has been discussed in detail above (see Figures 2e, 2f, and 5).

For fluid extraction, a knowledge of concentrations in $g \cdot cm^{-3}$ is more informative than mole or mass fractions. For calculating the concentrations c of the equilibrating phases additional pVT data would be necessary. Unfortunately there is a great lack of such data for all systems that are of interest for fluid extraction. One of the few examples known is presented in Figure 9 (measurements by *Reamer* and *Sage*[24]). Here the pressure (composition) isotherm at 37.8 °C for CO_2 + decane is plotted three times: as a function of mole fraction x (Figure 9a), of concentration c of the hydrocarbon in $g \cdot cm^{-3}$ (Figure 9b), as well as of $\log c$ (Figure 9c)[25]. Point A corresponds to the concentration of the decane in

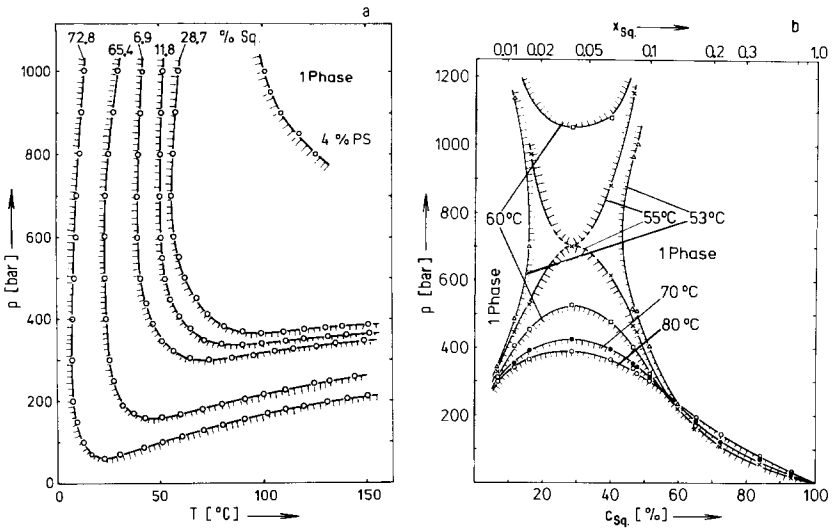


Fig. 8. Fluid phase equilibria in the system CO_2 + squalane (sq.). a) $p(T)$ isopleths, b) $p(c)$ or $p(x)$ isotherms (concentrations in weight percent), PS = polystyrene 600 (for comparison) (according to [14]).

the gas phase before adding CO_2 (that is to the concentration that results from the vapor pressure of pure decane in the gaseous phase) and point B to the concentration in $g \cdot cm^{-3}$ in pure liquid decane. In Figures 9b and 9c the branch on

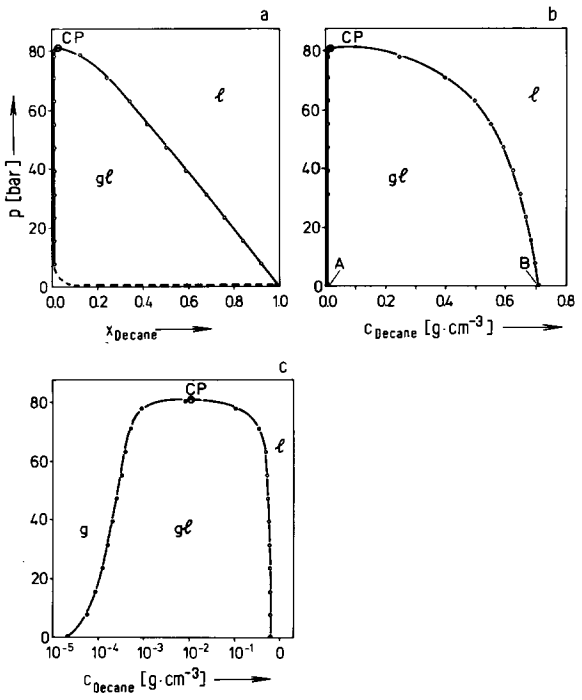


Fig. 9. Pressure (composition) isotherms of CO_2 + decane at 37.8 °C (according to *Reamer* and *Sage*[24]). a) $p(x)$ isotherm, b) $p(c)$ isotherm, c) $p(_{10}\log c)$ isotherm (see [25]).

the left gives the concentration of decane in the gaseous phase; it is increased by a factor of about 10^3 when raising the partial pressure of CO_2 from 0 to about 75 bar. Figure 9c demonstrates the high increase in decane concentration that can be obtained with increasing carbon dioxide pressures. Here the very rapid increase in the immediate neighborhood of the binary critical point CP of the isotherm is especially remarkable; for $p > p_c$ decane and CO_2 are even miscible in all proportions resulting in an infinitely high solubility of decane in CO_2.

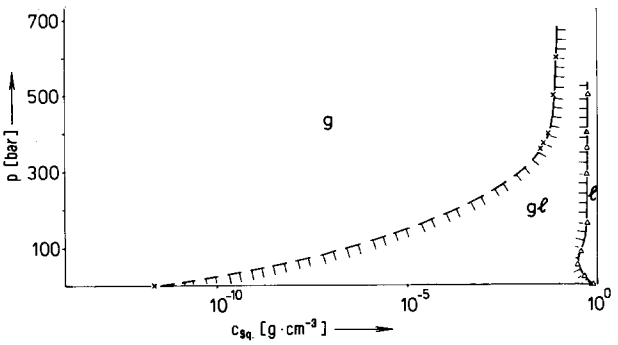


Fig. 10. $p(c)$ isotherm of CO_2 + squalane (sq.) at 40 °C (according to [14]).

This effect is even much more pronounced for the system CO_2 + squalane[14] in Figure 10: the squalane concentration in the gaseous phase is increased by a factor of about 10^{10} on raising the CO_2 pressure from 0 to about 400 bar; for the isotherm given, however, the mutual miscibility does not become complete as the pressure of CO_2 increases further but on the contrary a decrease of mutual miscibility is found.

Figures 9c and 10 demonstrate the rapidly increasing solvent power of highly compressed carbon dioxide and other fluids with increasing pressures, as is extensively exploited in fluid extraction. The short part of the isopleth for 4 wt % of polystyrene in CO_2 shown in Figure 8a demonstrates that relatively low-molecular material can be extracted with supercritical CO_2 from a polymeric substance.

In Figure 11 the $p(T)$ projections of the phase diagrams for binary mixtures of CO_2 with some normal alkanes of very different chain length (between 1 and 30 carbon atoms) are presented[13, 14]. The critical $p(T)$ curves (thick solid lines) have a very different shape and correspond to many of the types schematically given in Figure 2, *e.g.* to type 1 in Figure 2b (methane + CO_2, CO_2 + butane, CO_2 + pentane, CO_2 + octane (lg), CO_2 + decane (lg), CO_2 + undecane (lg)), to type 2 in Figure 2b (CO_2 + propane), to type 3 in Figure 2b (CO_2 + ethane; exhibition of critical azeotropy), to the type in Figure 2c (CO_2 + octane (lg and ll), CO_2 + undecane (lg and ll)) and to the type in Figure 2e (CO_2 + hexadecane,

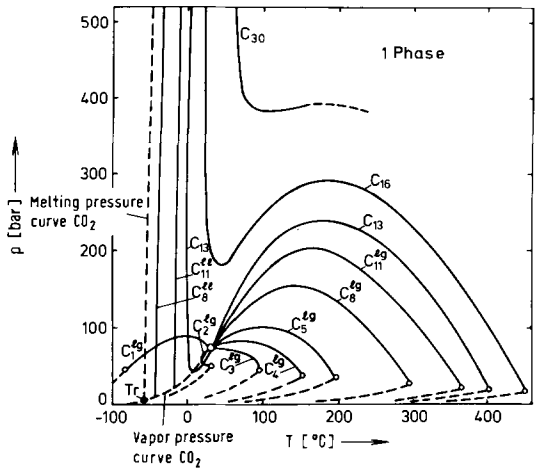


Fig. 11. $p(T)$ diagrams of CO_2 + n-alkanes ($C_n = n$-C_nH_{2n+2} for $n = 1$ to 16; C_{30} = squalane; for details and references see text; cf. [7]).

CO_2 + squalane). The critical $p(T)$ curves of the two last-mentioned systems run through temperature minima and thus resemble those of systems with gas-gas equilibria of the 2nd kind (see type 2 in Figure 2h). For a detailed discussion and numerous references, see [7].

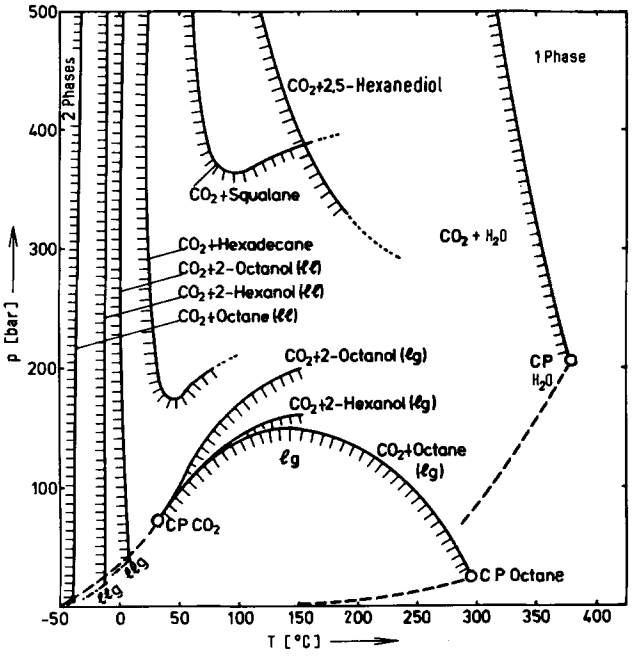


Fig. 12. $p(T)$ diagrams for binary mixtures of CO_2 with alkanes, alkanols, and water (for details and references, see text; cf. [7]).

In Figure 12 some curves already given in Figure 11 and also parts of the critical $p(T)$ curves of the systems CO_2 + 2-hexanol (lg and ll)[9], CO_2 + 2-octanol (lg and ll)[9], and CO_2 + 2,5-hexanediol[9] as well as of CO_2 + water[26] are plotted. Whereas the phase behavior of CO_2 + 2-hexanol and CO_2 + 2-octanol corresponds to the type in Figure 2d (such as CO_2 + octane, *etc.*), the system CO_2 + water belongs to type 2 in Figure 2h (with gas-gas equilibria of the 2nd kind), and CO_2 + 2,5-hexanediol has to be attributed to an intermediate type.

In Figure 13 the critical $p(T)$ curves of some binary C_2H_6 systems are given where the low-volatile component II is varied systematically[9]. Whereas C_2H_6 + methanol belongs to type 2 in Figure 2f and C_2H_6 + water[27] to type 2 in Figure 2h (corresponding to a gas-gas equilibrium of the

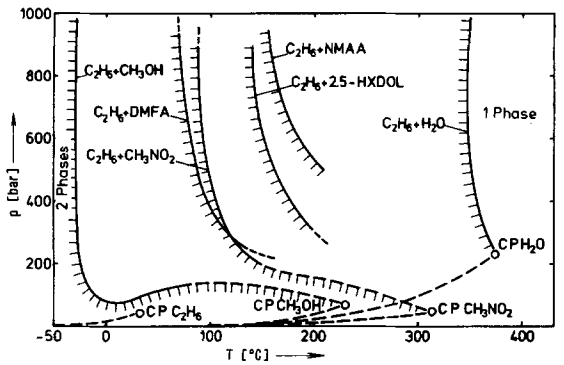


Fig. 13. $p(T)$ diagrams for binary mixtures of C_2H_6 with organic compounds (DMFA = dimethylformamide; NMAA = *N*-methylacetamide; 2,5-HXDOL = 2,5-hexanediol; for details and references, see text; cf. [9]).

2nd kind) all other systems show intermediate types of phase behavior (*e.g.*, C_2H_6 + nitromethane corresponds to type 1 of Figure 2h).

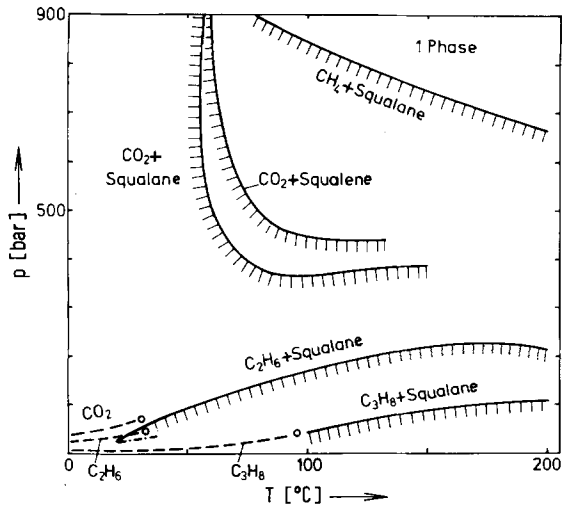


Fig. 14. $p(T)$ diagrams of binary mixtures of squalane with CH_4, C_2H_6, C_3H_8, and CO_2 and for CO_2 + squalene (for details and references, see text).

In Figure 14 the critical $p(T)$ curves for binary mixtures of squalane (component II) with methane, carbon dioxide, ethane, or propane (component I) as well as the critical $p(T)$ curve of CO_2 + squalene are presented; here, in contrast to Figures 11—13, the high-volatility component I is varied. Whereas the CH_4 + squalane system[28,29] exhibits a critical curve of type 2′ in Figure 3d (or type 1 in Figure 2h), the systems CO_2 + squalane[14] and CO_2 + squalene[28] correspond to type 3 in Figure 2f with a temperature minimum on the critical curve. For C_2H_6 + squalane type 3a and 3b was found[30,31,29]; here the part of the miscilitity gap that corresponds to upper critical solution temperatures (UCST) is situated at temperatures below the crystallization surface and can only be reached in undercooled melts[29]. The system C_3H_8 + squalane belongs to the simple type of Figure 2b[28].

Figures 11—14 demonstrate the very different types of phase diagrams for mixtures of CO_2 or ethane with organic substances of different molecular size, shape, structure, and/or polarity. Very similar phenomena have also been found for

binary mixtures of ethylene[9], methane[7, 32], or inert gases[33, 34], and even of water[4, 7, 35, 36] or ammonia[37] in a wide temperature range between about 100 and 700 K but in a comparable pressure range up to some kbar (for a review, see [7]). Figures 11—14 thus demonstrate the diversity and complexity of phase behavior in mixtures that are of importance for fluid extraction. This complexity makes predictions difficult and at least some informative measurements are recommended. Furthermore it follows from Figures 12 and 13 (for similar plots see [7, 9]) that supercritical gases (*e.g.* CO_2 or C_2H_6) are not all "super-solvents" for nearly all substances but, on the contrary, relatively poor solvents (*e.g.* in comparison with many liquids). Depending on pressure and temperature they have, however, a very selective and highly pressure-dependent solvent power for substances of medium molecular mass and relatively low polarity such as found for some important natural products (for a systematic discussion of this point, see *Stahl*[17]). This variable but limited solvent power is an important advantage and without it no selective extraction (*e.g.* of caffeine from coffee or of nicotine from tobacco[15]) would be possible.

3.3. Applications in Supercritical Fluid Chromatography (SFC)

The increasing solvent power of carbon dioxide for organic substances with increasing pressure can be easily demonstrated in SFC experiments. In this relatively new chromatographic technique highly compressed fluid phases mostly at temperatures somewhat above their critical temperatures are used as mobile phases especially for the separation of substances with a very low volatility and/or too low a thermal stability to allow a normal GC separation. The influence of varying the pressure of the mobile phase is shown in Figure 15 where SFC chromatograms for the migration of hexadecane with CO_2 as a mobile phase at 40 °C and different pressures are given according to measurements of *van Wasen*[41]. A pressure increase from 73 to 87 bar raises the migration rate of the organic compound in the column by a factor of about 10.

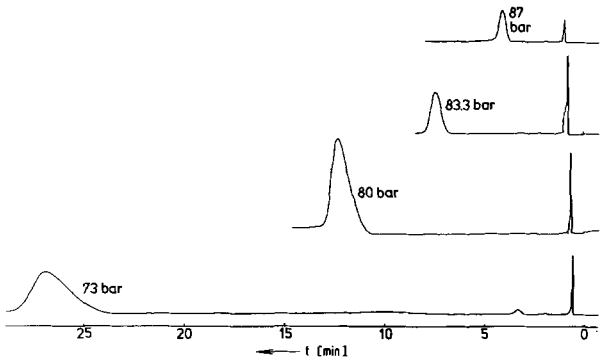


Fig. 15. Supercritical fluid chromatography (SFC) with supercritical CO_2 as mobile phase: retention times of hexadecane at different pressures of CO_2 (according to [41]); CO_2, 40 °C, 0.5 dm^3 (NTP)·min^{-1}; stationary phase: Carbowax 400 (chemically bonded on Porasil C); column length 2 m, diameter 1.4 mm; sample size 0.2 µl).

Some physicochemical properties can be derived from SFC experiments: *e.g.* the capacity ratio k_i of a component i that can be calculated from equation (1) with the retention time t^0 of an inert substance and the retention time t_i^r of the substance i under test

$$k_i = \frac{c_i^{stat}}{c_i^{mob}} \cdot \frac{V^{stat}}{V^{mob}} = K_i \frac{V^{stat}}{V^{mob}} = \frac{t_i^r - t^0}{t^0} \quad (1)$$

The capacity ratio k_i is proportional to the partition coefficient K_i and thus characteristic for the elementary separation effect; V^{stat} and V^{mob} are the volumes of the stationary and the mobile phases in the column respectively.

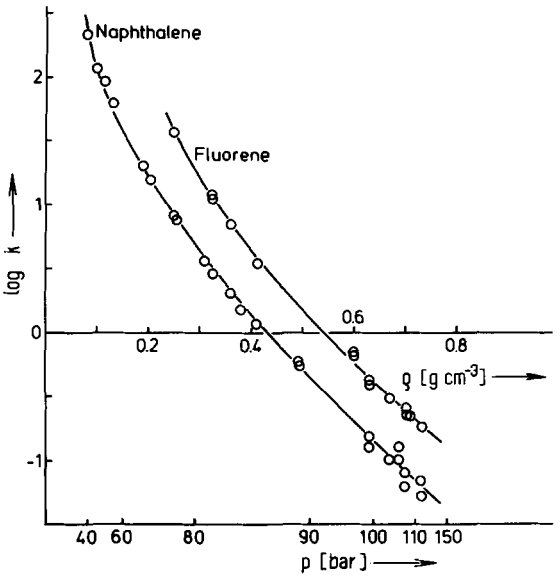


Fig. 16. Supercritical fluid chromatography (SFC) with supercritical CO_2 as a mobile phase: Density and pressure dependence of the capacity ratio k for naphthalene and fluorene (according to [41]); 40 °C, 0.7 dm^3 (NTP) · min^{-1}; stationary phase 3.1 g Perisorb A.

In Figure 16 the logarithms of some experimental k-values are plotted against the density ρ (linear abscissa) and the pressure p of supercritical carbon dioxide at 40 °C as a mobile phase for SFC experiments on naphthalene and fluorene according to *van Wasen*[41]. It follows that with a density increase from 0.1 to 0.8 g·cm^{-3} the capacity ratio k_i and the partition coefficient K_i decline by a factor of about 10^4, corresponding to an enormous increase of the concentration in the mobile phase. As is usually found, the plot of $\log k_i$ *versus* $\rho(CO_2)$ better approaches a straight line than does that *versus* $p(CO_2)$[42]. However, this analogy between solvent power and density should not be over-interpreted since a decrease of solubility with increasing density is also frequently found (*e.g.* for type 2 in Figure 2d, for type 3 in Figure 2f, for types 2 and 3 in Figure 2h).

Figure 16 demonstrates the large change in solvent power of supercritical CO_2 and other fluids as a function of density and pressure such as used in fluid extraction and SFC. In comparison with normal GC, SFC is advantageous for the separation of thermally labile and/or low-volatility substances because of the lower separation temperatures and the use of pressure programs (instead of temperature programs as in GC). In comparison to HPLC, SFC will in general be less effective for analytical purposes but it may have considerable advantages for preparative applications mainly because of easy reprecipitation of the separated pure substances from the mobile phase (*e.g.* by decreasing pressure or freezing out). For a detailed discussion of SFC see *Klesper*[43], *Gouw* and *Jentoft*[44], *Bartmann* and *Schneider*[25]).

4. Calculation of Phase Equilibria in Fluid Mixtures

Because of the important applications mentioned above, methods for the calculation and correlation of the thermodynamic properties of fluid mixtures at high pressures (*e.g.* the phase diagrams) are of increasing interest; this fact is demonstrated by an increasing number of publications in this field in recent years.

The calculation methods start with the fact that the conditions for phase equilibria and for critical points are essentially the same for all types of two-phase equilibrium in fluid mixtures: namely liquid-gas, liquid-liquid, and gas-gas. In a binary mixture, two phases (′ and ″) are in equilibrium if the following equations hold

$$p' = p'' \tag{2}$$

$$T' = T'' \tag{3}$$

$$G'_m - x'_i \cdot (\partial G_m/\partial x_i)'_{p,T} = G''_m - x''_i \cdot (\partial G_m/\partial x_i)''_{p,T} \tag{4}$$

with $i=1$ and 2, or condition (4a) that is equivalent to (4)

$$\mu'_i = \mu''_i \tag{4a}$$

G_m is the molar Gibbs energy and μ_i the chemical potential of component i in the mixture.

A binary critical point is defined by

$$(\partial^2 G_m/\partial x_i^2)_c = 0 \tag{5}$$

$$(\partial^3 G_m/\partial x_i^3)_c = 0 \tag{6}$$

From the phase equilibrium conditions (2), (3), and (4) or (4a) the phase diagram and from conditions (5) and (6) the binary critical curve can be calculated. In most cases, however, the more complicated corresponding conditions for the molar Helmholtz energy A_m (instead of the molar Gibbs energy G_m) have to be used.

G_m or A_m can be obtained:

a) from an equation of state that is often a modified version of the Redlich-Kwong or the van der Waals equation using sometimes rather sophisticated combining rules for the parameters,

b) from theories of mixtures starting from models with the use of different combining rules for the potential parameters in the mixture, or

c) for liquid-gas and liquid-liquid equilibria up to moderately high pressures using equations for the excess functions in the liquid phase (*e.g. Porter, van Laar, Wilson*, NRTL, UNIQUAC, *Flory-Huggins* and others or using group contributions, *e.g.* ASOG and UNIFAC[2,45,46]).

Such calculations require not only a good representation of the phase equilibria but also of *pVT* data and caloric properties. Much of this field has recently been reviewed by *Prausnitz*[47,48]. Calculations and references have been given by *Schneider*[7], *Deiters et al.*[49], *Deiters*[72], *McGlashan et al.*[50], *Twu et al.*[51], *Young et al.*[52], *Peter et al.*[53,55], *Huron et al.*[54], *Smith et al.*[77], and others. The reader is referred to the literature for details; for a review, see [45].

Only two examples are presented in Figure 17 where, for $C_2H_4+CH_3NO_2$ (Figure 17a) and C_2H_6+dimethylformamide (DMFA) (Figure 17b), the critical $p(T)$ curve calculated by *Deiters et al.*[49] from the Redlich-Kwong equation is compared with measurements of *Alwani*[9]. Figures 17a and 17b show that even systems belonging to type 1 in Figure 2f (Figure 17a) or to type 1 in Figure 2h (Figure 17b) can be calculated in good agreement with experimental data. Considerable progress can be expected in this field within the next few years.

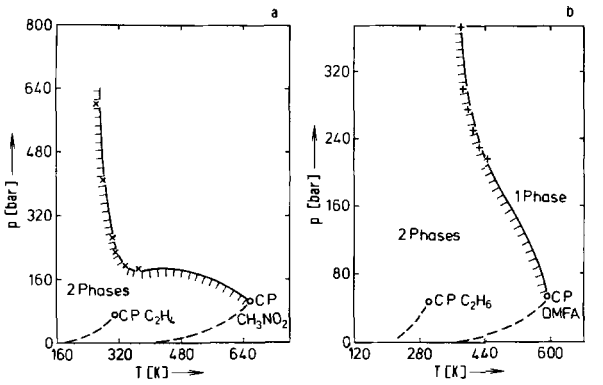


Fig. 17. $p(T)$ diagrams for a) C_2H_4 + nitromethane and b) C_2H_6 + dimethylformamide (DMFA): Comparison of experimental (×) [9] and calculated values (–) [49].

5. Selected Physicochemical Properties

Besides phase equilibria (see Sections 2—4), some other physicochemical properties (*e.g. pVT* data, viscosities, diffusion coefficients, *etc.*) are also of fundamental importance for a separation process such as fluid extraction. Since there is a great lack of experimental data in this field, some remarks concerning the most important properties only will be given in the following.

5.1. *pVT* Data and Dielectric Constant

Figure 18 shows some $p(\rho)$ isotherms for pure carbon dioxide at subcritical and supercritical conditions; here reduced vari-

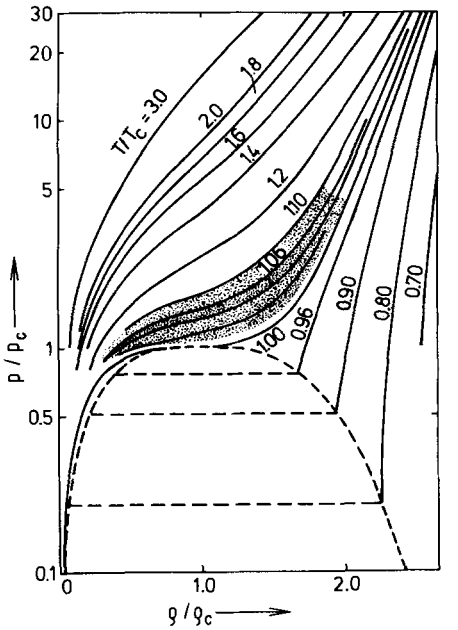


Fig. 18. $p(\rho)$ isotherms for pure carbon dioxide. p_c, T_c, and ρ_c are critical data; region of interest for fluid extraction is dotted.

ables are used and the region that is of interest for fluid extraction is shown dotted. For $T > T_c(CO_2)$ the density increases rapidly with rising pressure and at the critical point CP $(\partial\rho/\partial p)_T = \infty$[1].

In Figure 19 the density ρ and the static dielectric constant ε for carbon dioxide[8, 56] and argon[57, 58] are compared with respect to their dependence on pressure. In Figure 19a, ε is plotted against pressure up to 2000 bar; $\varepsilon(CO_2)$ increases from 1 to about 1.8 (322.9 K) and ε(Ar) from 1 to 1.4 (298 K). This effect also provides evidence for the greater solvent power of supercritical carbon dioxide for low-volatility compounds at elevated pressure.

For substances without permanent dipole moments ρ and ε are related according to the Clausius-Mosotti equation [eq. (7)]

$$P_M \equiv \frac{\varepsilon - 1}{\varepsilon + 2} \cdot \frac{M_r}{\rho} = \frac{1}{3 \cdot \varepsilon_0} \cdot N_L \alpha \qquad (7)$$

Numerous literature data demonstrate that, up to moderately high pressures, the molar polarization P_M defined by equation (7) is essentially independent of pressure. A constant value of the polarizability α follows from this finding; thus α is practically uninfluenced within the pressure range that is relevant for fluid extraction.

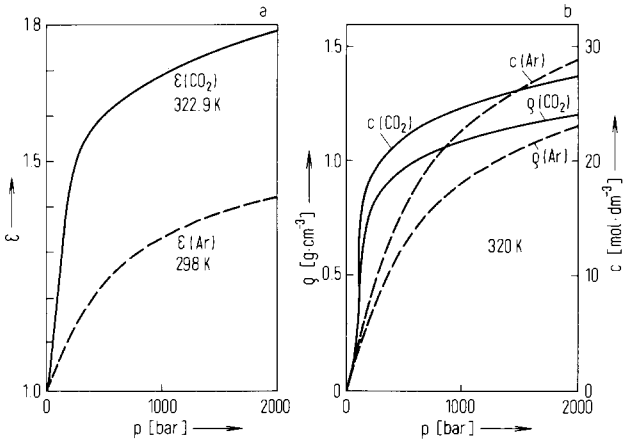


Fig. 19. Comparison of the pressure dependence of density ρ, concentration c, and (static) dielectric constant ε for pure CO_2 and Ar (see [8, 56, 58, 72]).

In Figure 19b the density ρ and the concentration c are plotted against pressure p at 320 K for carbon dioxide[8, 72] and argon[57, 72]. For carbon dioxide both isotherms rise steeper than those for argon at the beginning but they then turn off and at about 1450 bar the $c(p)$ isotherms of the two substances intersect, whereas for the two corresponding $\rho(p)$ isotherms an intersection point can be extrapolated at about 2900 bar. In spite of similar densities, however, the solubility of organic substances in compressed argon is normally smaller than that in carbon dioxide by several orders of magnitude and can already widely be understood in view of the vapor pressure increase of a condensed substance under high inert gas pressures only ("Poynting effect"; see [2]). Thus Figure 19b demonstrates that the solvent power of supercritical fluid phases cannot exclusively be explained from their density increase.

5.2. Transport Properties

For very small concentrations of substance II to be purified the transport properties of the pure solvent gas (component I) will give some information about the orders of magnitude involved. In Figure 20 the density ρ, the viscosity η and the product $D_{11} \cdot \rho$ (where D_{11} = self-diffusion coefficient) of pure carbon dioxide are plotted against pressure up to 500 bar and at 40 °C (that is about 9 K above T_c) according to data taken from the literature (for references, see [25]).

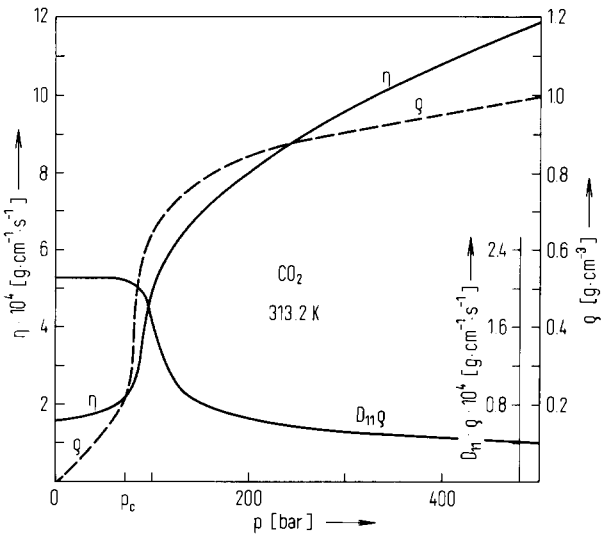


Fig. 20. Density ρ, viscosity η, and $D_{11} \cdot \rho$ for pure CO_2 as a function of pressure at 40 °C (according to literature data [25]; D_{11} = self-diffusion coefficient).

In agreement with simple kinetic theory, η and $D_{11} \cdot \rho$ remain essentially constant up to about 80 bar. As the pressure rises further, an increase of η and a decrease of $D_{11} \cdot \rho$ are found. At 400 bar the following ratios are obtained $\eta(400\,\text{bar})/\eta(1\,\text{bar}) \approx 7$ and $D_{11}(400\,\text{bar})/D_{11}(1\,\text{bar}) \approx 4 \times 10^{-4}$. Thus fluid extraction can profit from relatively low viscosities in the gaseous phase as well as from diffusion coefficients that are considerably higher than the usual values for liquids ($D_{11} < 10^{-5}\,\text{cm}^2 \cdot \text{s}^{-1}$).

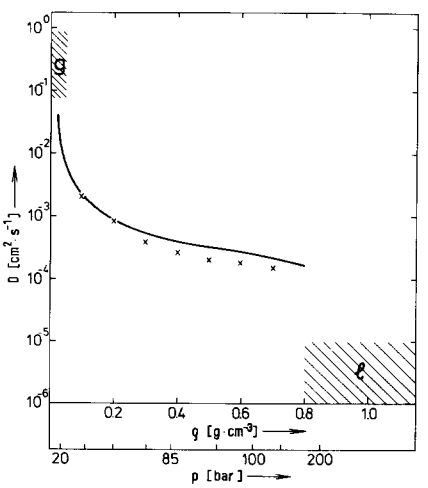


Fig. 21. Self-diffusion coefficient D_{11} of CO_2 at 42 °C (according to [71]) and binary diffusion coefficient D_{12} of benzene in CO_2 at 40 °C (×) [41] as a function of density ρ or pressure p.

The same tendency can be deduced from the rare literature data for the binary diffusion coefficients D_{12} in such mixtures at high pressure. Figure 21 shows D_{12} values for benzene in carbon dioxide at 40 °C as a function of density and pressure as determined with the aid of a chromatographic method by *van Wasen*[41]. A density and pressure dependence similar to that for D_{11} of pure carbon dioxide is obtained. The D_{12} values are smaller than those in a normal gaseous phase at 1 bar by about 2 to 3 orders of magnitude; they are, however, still about 1.5 orders of magnitude above those in normal liquids. Qualitatively similar results on D_{12} of butane in compressed argon were obtained by *Giddings et al.*[59], and for that of naphthalene in compressed carbon dioxide by *Vinkler et al.*[81].

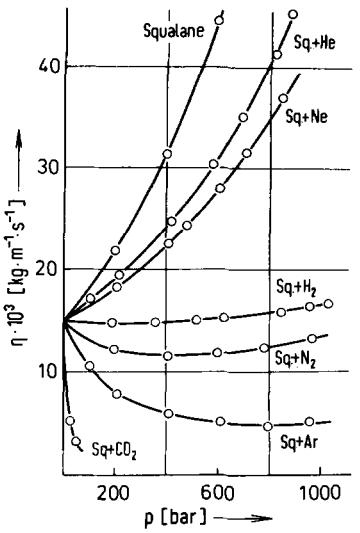


Fig. 22. Pressure dependence of the viscosity η of squalane (sq.), pure and saturated with various gases (according to [60]).

Favorable transport properties can also be estimated for the phase rich in component II. In Figure 22 the viscosity of squalane (pure and saturated with various gases such as helium, neon, hydrogen, nitrogen, argon, and carbon dioxide) at 40 °C and up to 1000 bar is plotted according to measurements of *Kuss et al.*[60]. It is seen that the increase of viscosity with rising pressure becomes considerably smaller for a liquid when gases are dissolved in it, and because of their high solubility even a decrease of viscosity is found for squalane saturated with nitrogen, argon, and carbon dioxide. Since D should be proportional to $1/\eta$ far away from critical states, relatively high diffusion coefficients can also be expected. Therefore the phase rich in component II again shows relatively low viscosities and high diffusion coefficients which are both favorable for separation methods such as fluid extraction or SFC. This is an additional advantage of these methods over liquid extraction and HPLC.

6. Outlook

Fluid mixtures, especially in the critical and supercritical region, are becoming increasingly important in many fields. Characteristic for the situation is the recent foundation of a journal entitled "Fluid Phase Equilibria". (For the recent literature, see [61].)

Fluid aqueous mixtures at high pressures are of fundamental interest in geology and mineralogy, *e.g.* in the formation and migration of minerals, gases, or petroleum in the mantle of the earth, for research on volcanos and geysers, for hydrothermal synthesis, *etc.* The solubilities of many inorganic substances in supercritical water have been measured (for a review, see [21, 62]).

In astronomy and space research, fluid phase equilibria of mixtures (*e.g.* also gas-gas equilibria) play an important role in the atmospheres of some planets[63].

In chemistry highly compressed supercritical gases are of increasing importance as reaction media of continuously variable density, dielectric constant, and solvent power; here the supercritical gas can be solvent as well as reactant, *e.g.* C_2H_4 (especially in the synthesis of polyethylene), NH_3[64], CO_2[65], Cl_2[66], F_2[68]. They are also of interest for some industrial high pressure syntheses, *e.g.* of ammonia, methanol, acetic acid, polyethylene, as well as in the oxo synthesis and in the Fischer-Tropsch process[67].

Fluid phase equilibria at high pressures are of fundamental importance in the petroleum and natural gas industry, *e.g.* for the exploitation of wells, for separation and purification methods (also under cryogenic conditions), or for the storage and transport of products.

Direct applications have already been implemented in fluid extraction and supercritical fluid chromatography treated in the present issue of this Journal. Extraction of coal with supercritical toluene appears promising[78–80]. A patent has already been granted for a method for desalination of sea water with isopropylbenzene which utilizes gas-gas equilibria[69]. Supercritical water has been considered as an extractant for aromatic hydrocarbons from mixtures with straight-chained and branched alkanes[70]. For the exploitation of mineral springs and the production of carbonated beverages, phase equilibria of the kind discussed in Sections 2—4 are of fundamental interest[*]. Moreover, supercritical carbon dioxide is a very mild drying agent, *e.g.* for tissue sections.

Since there will certainly be further applications in the near future, it seems worthwhile to stimulate interest in the physicochemical properties of fluid mixtures at high pressures. These properties are largely unknown up to now and really merit extensive investigation, particularly since the ranges of temperatures and pressures involved in such studies are already accessible owing to rapid developments in experimental high pressure techniques.

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[*] According to *Tödheide* and *Franck* [26], the $p(T)$ phase diagram of $CO_2 + H_2O$ corresponds to type 2 in Figure 2h. $p(x)$ isotherms for $T > T_c(CO_2)$ (*e.g.* under conditions occurring in summer in a bottle of mineral water) will resemble those presented schematically in Figures 5b—5d.

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Phase Equilibria and Critical Curves of Binary Ammonia–Hydrocarbon Mixtures[**]

By Harro Lentz and Ernst Ulrich Franck[*]

Liquid or dense supercritical ammonia has been suggested as an extraction fluid. It is indeed a good solvent for very different classes of compounds, as can be seen from phase diagrams. Such diagrams for binary systems of ammonia and hydrocarbons are presented and discussed on the basis of their critical curves. Apparatus and methods for the measurement of phase equilibria and equation of state data of fluid mixtures at high pressure are described.

1. Introduction

Ammonia is one of the compounds suggested as a mobile phase for extraction and chromatographic processes[1]. It is a good solvent, particularly for nitrogen-containing compounds, and has a convenient critical point ($T_c = 132.24$ °C, $P_c = 113.53$ bar, $V_c = 72.8$ cm^3 mol^{-1}). Evaluation of possible applications as extractant requires a knowledge of phase equilibria, critical phenomena, and thermodynamic functions of binary systems of ammonia and selected, typical hydrocarbons. Experimental results of this kind as well as methods and equipment will be described here.

Ammonia–nitrogen[2,3] was the first system for which vapor–liquid equilibria and the critical behavior were investigated experimentally up to high pressures. Measurements on ammonia–argon[4,5] and ammonia–helium[6] were published later. These systems have discontinuous critical curves, while the ammonia–water system has a continuous critical curve[7]. An exhaustive study of the phase equilibria in the ammonia–carbon dioxide system has so far been precluded by chemical interaction[8].

Phase equilibria and critical phenomena are known for the following ammonia–hydrocarbon mixtures: NH_3–methane[9,10], NH_3–ethane[11–13], NH_3–*n*-butane[14], NH_3–2,2,4-trimethylpentane[15], NH_3–cyclohexane[16], NH_3–*o*-xylene[17], and NH_3–acetylene (in part)[18]. Very recently studies have been made on NH_3–ethylene[19], NH_3-propylene[20], NH_3–benzene[21] and NH_3–*trans*-decalin[22].

2. Apparatus and Methods

Phase equilibria have been determined using both the "analytical" and the "synthetic" method.

In the analytical method, samples taken from the coexisting phases are analyzed. A one-liter stainless steel vessel is suitable for equilibration up to pressures of about 200 bar. The contents are stirred magnetically and the internal temperature measured by two miniature sheathed thermocouples. Pressure is generated by a hydraulic pump and measured by precision Heise-Bourdon gauges. Several other designs of apparatus for the analytical method have been described for higher pressures[23–25].

In the synthetic method, a mixture of known composition is filled into the vessel and the disappearance of phases observed. Apparatus for this method is less common. However, the method permits simultaneous determination of volumes and hence of molar concentrations which are of value, for example, in chromatographic applications.

Figure 1 shows a one-window equilibrium cell for measurements to 3 kbar and 500 °C[26]. The sample is located between a window of colorless synthetic sapphire and a movable piston. The sample volume can easily be changed and measured by moving the piston and determining its position. At the rear of the piston is a pressurizing fluid, which may be water, and which serves to determine the sample pressure, because both pressures are very nearly equal. Attached to the piston is a thin steel rod with a magnetic tip, reaching into the nonmagnetic high pressure capillary through which the pressurizing fluid is fed into the vessel. The position of the tip is determined from outside by an inductive bridge with a pair of coils on a straight rule with a vernier scale. The front of the piston carries a platinum mirror which facilitates visual observation of the whole sample through the sapphire window. The front part of the autoclave, containing the window, can be separated from the main body. Sealing is achieved by means of a double cone and a left-hand and a right-hand thread. High pressure cell, piston, and the sealing double cone are made from a high-strength nonmagnetic nickel alloy (DEW ATS 340). A small magnetic stirrer within the sample space can therefore be agitated from the outside. Close to the window, two holes and high pressure connections serve for sample introduction and to accommodate a sheathed thermocouple. The autoclave is surrounded by a resistance heater divided into several sections, so that a uniform temperature can be produced in the sample space and—if necessary—a lower temperature can also be ensured at the rear O-ring of the long piston.

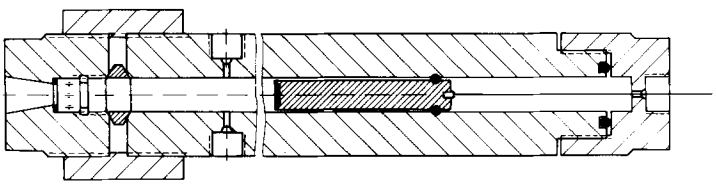


Fig. 1. High pressure cell for measurement of phase equilibria, and *P,V,T*-data at high pressures and temperatures. Left-hand side: removable part with sapphire window. Right-hand side: main body of the cell with movable piston (see text).

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Ammonia and hydrocarbon are introduced from reservoirs into the high pressure cell and the amounts transferred are determined by weighing.

At constant volume, *i.e.* at constant position of the piston, the temperature is raised slowly and the temperature and pressure values are recorded. Phase transitions are indicated as break points of the isochoric curves thus obtained, and can be verified by visual observation through the sapphire window. The pressure is generated by means of a spindle press filled with the pressurizing fluid, and it is measured by precision Bourdon gauges or strain gauge pressure transducers. In the region of homogeneous behavior of the mixture, *P,V,T*-data could also be determined in this way with relative ease. This had been done previously with acetonitrile[27], benzene[28], *n*-pentane[29], and with the binary mixtures water-argon[30] and water-xenon[31].

Another type of apparatus shown in Figure 2 is simpler since it does not need any additional high pressure equipment. It can be used up to 150°C and 2 kbar, and permits phase observations as well as volume determinations (Hofer Hochdruck GmbH, Mülheim-Ruhr). The lower part is an optical cell with two sapphire windows of 10 mm diameter and O-ring packings. Pressure is generated with a hand-operated piston in the upper part and is measured with a small strain gauge transducer. The position of the piston, and hence the sample volume are directly measurable. The temperature is adjusted by means of a thermostated heating jacket. A thermocouple is located inside the sample space or within a bore close to the sapphire window. Liquids can be filled into the cell directly while gases can be fed in *via* a valve replacing the blind closure shown on the left-hand side of Figure 2. Melting pressure curves[32] as well as the liquid-liquid phase separation of the system ammonia-ethylene have been determined with a cell of this design.

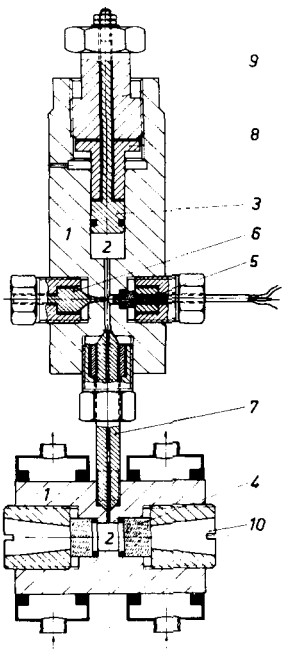


Fig. 2. Optical cell with an attached high pressure generator. 1, cell body; 2, sample space; 3, pressure generating piston; 4, sapphire windows; 5, pressure transducer; 6, blind closure; 7, connecting capillary; 8, pressure ring; 9, screw to generate pressure; 10, window support.

3. Results

The shape and position of the critical curve contain essential information on the phase behavior of a binary system. Such curves may simply connect continuously the two critical points of the pure components. If both components have very different properties, the critical curve may be broken. The lower branch begins at the critical point of the low-boiling partner and may find a "lower critical end point" on a three-phase curve (liquid-liquid-gas). The upper branch of the curve starts at the higher critical point and proceeds to higher temperatures and pressures. It may exhibit extreme values of pressure.

Figure 3 shows a number of gas-liquid critical curves of binary ammonia–hydrocarbon systems. With the exception of ammonia–methane, all systems show continuous curves. Temperature minima and—very probably azeotropy up to the critical region—occur for ammonia in combination with ethane, propylene, butane, and 2,2,4-trimethylpentane. Pressure maxima have been found for ammonia together with cyclic compounds and with ethylene and 2,2,4-trimethylpentane. The curve of the last-named system appears to have a pressure minimum as well. Ammonia–ethylene, ammonia–*n*-butane and ammonia–2,2,4-trimethylpentane show inflection points. The critical curve for ammonia–methane has a temperature minimum at 44°C, 1080 bar, and 29.0 $cm^3 mol^{-1}$. The mixture

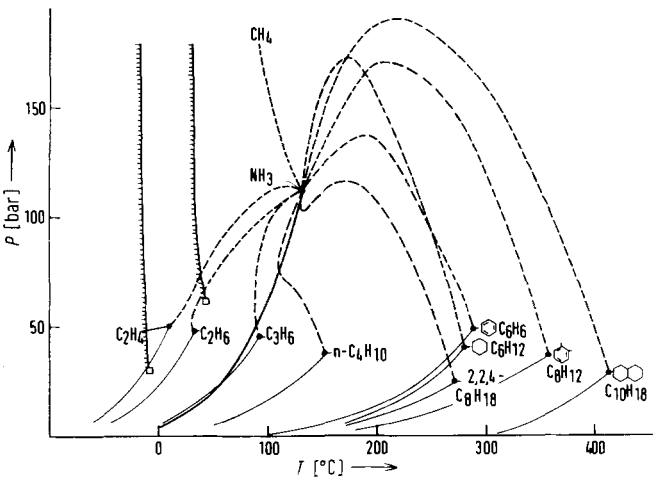


Fig. 3. Projection of critical curves on the pressure-temperature plane for binary ammonia–hydrocarbon mixtures. Liquid-vapor critical curves are dashed, liquid-liquid critical curves have horizontal marks, vapor pressure curves are shown as solid lines.

contains 44.5 mol percent methane at this point. Liquid-liquid critical curves for systems of this kind have so far only be determined for ammonia with ethane and ethylene (see Fig. 3).

The points on the critical curves are the locations of the maxima and minima of the equilibria isotherms and isobars on the phase interface in *P,T,x*-space. Figure 4 gives a set of such isotherms for ammonia–*trans*-decalin. Above 300°C chemical reactions impede the measurements, particularly in the liquid phase. Thus some isotherms had to be partly estimated (dashed curves in Fig. 4)[22].

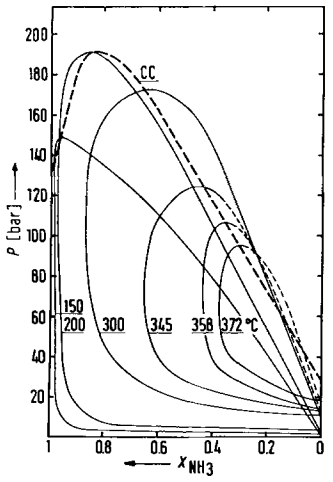


Fig. 4. Equilibrium isotherms for the ammonia–*trans*-decalin system. CC is the critical curve.

4. Discussion

The phase equilibria of several hydrocarbons have been investigated in combination with ammonia and with water. The critical temperature and pressure of water (374.15 °C, 221.3 bar, 57.4 cm^3 mol^{-1}) are considerably higher than those of ammonia. Accordingly, the phase diagrams for aqueous systems often differ in character from those of the ammonia systems. Ethane, butane, and benzene in aqueous systems have discontinuous critical curves. Figure 5 compares the phase behavior of methane[9, 10, 33, 34], ethane[11–13, 35], and benzene[21, 36, 37] in combination with ammonia and with water. A liquid-liquid miscibility gap is expected for ammonia–benzene but has not yet been verified experimentally.

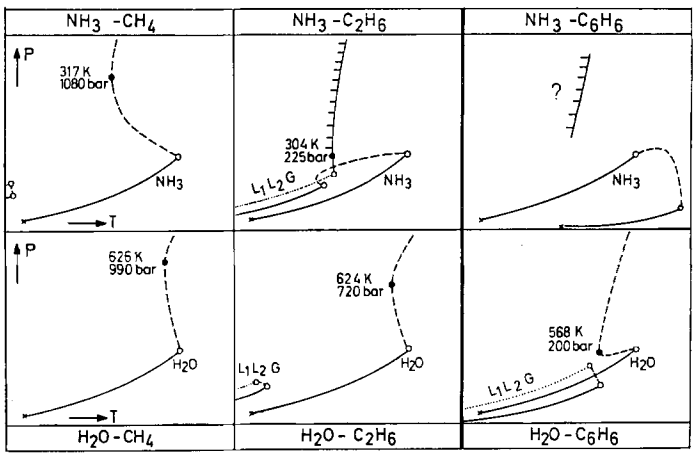


Fig. 5. Comparison of the phase behavior of binary systems with water or ammonia as polar component. Three-phase lines are dotted. Other curves are drawn as in Fig. 3.

The existing theoretical methods of describing and predicting the phase behavior of mixtures with polar components are still unsatisfactory. It appears, however, that data for ternary systems can be derived with reasonable dependability from a knowledge of the three relevant binary systems. Thus it is hoped that the results presented here might provide a useful contribution to the future application of ammonia for supercritical extraction purposes.

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A Quick Method for the Microanalytical Evaluation of the Dissolving Power of Supercritical Gases[**]

New analytical methods (12)

By Egon Stahl, Winfried Schilz, Erwin Schütz, and Eberhard Willing[*]

A new method of microextraction with supercritical gases involving direct coupling with thin-layer chromatography enables the solubility behavior of a large number of natural products to be investigated in pressure gradients of up to 400 bar. The results are summarized in general rules that enable the extractability to be predicted on the basis of the chemical structure. The substances that can be satisfactorily extracted in supercritical carbon dioxide and nitrous oxide are preferably lipophilic. The extracting capacity of the two gases was compared using alkaloids. In the case of polar compounds such as sugars and amino acids the solubility is so low even at pressures of 2500 bar (less than 10 μg/Nl) that application is not practicable. Quantitative tests of the solubility behavior of model substances in supercritical gases provide a basis for the technical application of the method.

1. Introduction

We were interested in new methods of separation for "solvent-free" microextraction of natural products and their direct transfer to a thin-layer chromatogram (TLC). Although solvent-free direct transfer is possible with the TAS process[1] and the thermofractography[2] described by us earlier, the action of heat is required in these cases. The temperatures needed for extraction are between 100 and 250 °C, so that the thermal stress on the substances is equivalent to that usual in gas chromatography. Since the transport is assisted by a carrier gas, the process can be regarded as carrier gas distillation on a microscale. We wanted to find a milder solvent-free method for the extraction of non-volatile and thermolabile natural products.

The inspiration came from fluid chromatography (cf. p. 738), which makes use of the fact that many substances that cannot be chromatographed under the normal conditions of gas chromatography despite the high temperature, because their vapor pressure is too low, can be transported at a relatively low temperature in supercritical gases. Our task was therefore to perform extraction with supercritical gases on a microscale, using TLC as the "detector".

Table 1. Physical data for a number of possible extractant gases.

Gas	At 1 bar B.p. [°C]	T_c [°C]	P_c [bar]	ρ_c [g/ml]	DC at 1 bar, 0 °C [ε − 1]
Carbon dioxide	− 78 (subl.)	31.3	73	0.448	0.0011
Nitrous oxide	− 89	36.5	71	0.457	0.00113
Ethylene	−103.7	9.5	50	0.20	0.0018
Chlorotrifluoromethane	− 81.4	28.8	39	0.58	0.0015
Trifluoromethane	− 82.2	25.9	46.9	0.516	—

The principal gases suitable for such extraction on account of their favorable critical parameters are carbon dioxide, nitrous oxide, ethylene, and special freons (Table 1).

The most attractive of these is carbon dioxide, which is easy to handle, ecologically unobjectionable, and reasonably priced. It can be seen from Figure 1 that the density and DC values rise steeply between 70 and 200 bar and reach values similar to those for liquids. This provides further explanation for the fact that several supercritical gases exhibit considerable solvent power above a certain pressure and can therefore be used in place of the usual solvents.

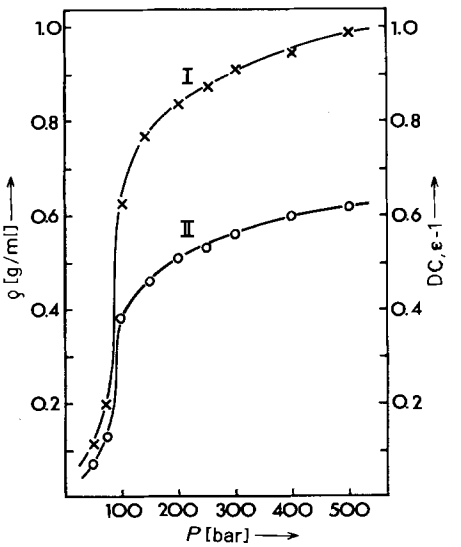


Fig. 1. Dependence of the density ρ(I) and the dielectric constant (II) of carbon dioxide at 40 °C on pressure.

The results that can be obtained are therefore of general interest. Basic research is important because it is difficult to gain access to some of the information obtained so far on extraction with supercritical gases, mainly because it is set out in patent applications or patents[3,4]. For this reason it was necessary to construct an installation for the microscale process so as to be able to test a large number of pure substances and more complex samples in a rational manner.

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[**] Based on a paper presented at the symposium "Extraction with Supercritical Gases", held in Essen on June 5, 1978.

2. Apparatus for and Function of Coupled Microextraction-TLC

The gas is taken from a commercial pressurized cylinder and its pressure is reduced to the desired preliminary level of 40—60 bar (Fig. 2).

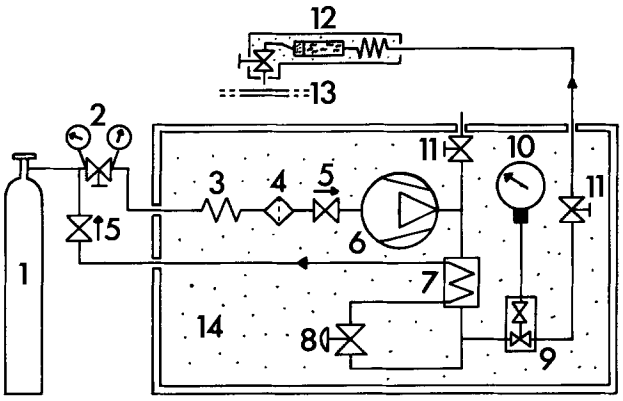


Fig. 2. Schematic layout of the apparatus for direct coupling of fluid extraction with thin-layer chromatography: 1) gas cylinder, 2) pressure-reducing valve, 3) preheating column, 4) filter, 5) check valve, 6) diaphragm compressor, 7) heat exchanger, 8) back-pressure regulator, 9) attenuators, 10) precision pressure gauge, 11) shut-off valve, 12) microautoclave for extraction, 13) TLC plate, 14) thermostatically-controlled container.

It is then compressed with the aid of an electrically driven diaphragm compressor to the desired pressure (70—400 bar). A back-pressure regulator accurate to within about 1 bar enables the pressure to be adjusted exactly; this is controlled by a precision pressure gauge. The compressor unit and the microautoclave are kept at a temperature of *e.g.* 40 °C with the aid of thermostats. The supercritical gas flows into the microautoclave, which has a capacity of 2 ml and contains the samples to be extracted. The outlet from the autoclave is closed by a miniature shut-off valve. When this valve is opened the supercritical gas charged with the substance flows out through a very fine capillary (internal diameter 50 µm), being decompressed in the process. The emerging stream of gas impinges on a TLC plate arranged horizontally 1—5 mm from the outlet. The plate is moved to and fro and collects the precipitating extracted substances as a starting band. As a rule we begin the extraction of a sample at 70 bar and allow 1 Nl (normal liter) of gas to pass through. The pressure is then raised in stages, generally of 10 or 20 bar, the TLC plate is shifted accordingly, the sample is again extracted with 1 Nl of gas, and so on. Figure 3 shows the apparatus for direct coupling of fluid extraction with TLC (FE-TLC); Figure 4 shows the microautoclave with the TLC plate fixed on a sliding support, the control unit, and the gas exhaust device.

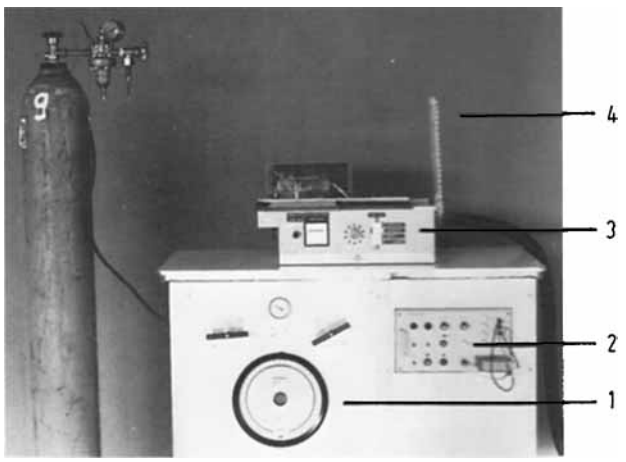


Fig. 3. Front view of the apparatus for direct coupling of fluid extraction with TLC (FE-TLC): 1) compressor station, 2) pressure control unit, 3) microautoclave with collecting device, 4) soap-bubble flowmeter.

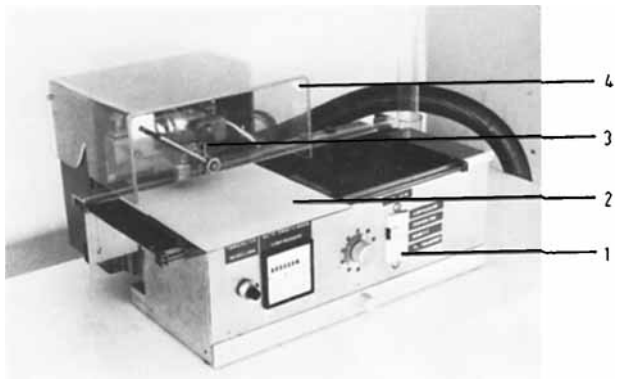


Fig. 4. Microautoclave with TLC collecting device: 1) control switches, 2) carrier slide with TLC plate, 3) microautoclave with shut-off valve, 4) perspex hood with exhaust device.

When the chromatogram has been developed it is possible to see the pressure at which the substance was extracted. It is also possible to tell from the varying intensity of the zones whether the quantity of substance extracted increases or decreases with increasing pressure.

The arrangement shown in Figures 2—4[5, 6] is suitable for use at up to a maximum of 400 bar. At higher pressures the emerging jet of gas damages the chromatographic layer and in addition the rebound effect is so great that only a small part of the extracted substances is collected. Another arrangement was therefore developed, which enables the substances to be collected quantitatively in both the lower and the higher pressure range (up to over 2000 bar). The apparatus is based on the same principle, except that instead of the TLC plate a collecting funnel filled with quartz wool is attached to the capillary tube. After the gas has been decompressed the substances precipitate in this collecting funnel and are extracted with a solvent; they can then be quantitatively determined directly, or applied onto a TLC plate, chromatographed in the usual manner, and then determined quantitatively.

3. Extraction of Difficultly Volatile Substances with Supercritical Gases

3.1. Study with Model Substances in the Pressure Range of up to 400 bar

As no information is yet available about the preconditions a substance must fulfil to be extracted with supercritical carbon dioxide, we first tested pure substances from several groups of natural products[6] (Table 2).

The compounds selected differed in respect of both their relative molecular weight and the number and nature of their functional groups. They ranged from nonpolar hydrocarbons to strongly polar substances. Evaluation of the results showed that a surprisingly large number of different types of substances

Table 2. Model substances extracted directly from quartz wool with supercritical carbon dioxide at 40 °C.

Substance	Rel. molecular weight	No. of C atoms	Functional groups	M.p. [°C]	B.p. [°C]	Extraction starts at [bar]
1. *Polyarenes*						
Naphthalene	128	10		80	218	70 strong
Phenanthrene	178	14		101	340	80
Pyrene	202	16		156	393	90
Chrysene	228	18		255	448	100 weak
Tetracene	228	18		357	subl.	300 weak
2. *Phenols*						
Phenol	94	6	1 —OH	43	181	70 strong
Pyrocatechol	110	6	2 —OH (1, 2)	105	245	80
Pyrogallol	126	6	3 —OH (1, 2, 3)	133	309	85
Hydroquinone	110	6	2 —OH (1, 4)	173	285	100
Phloroglucinol	126	6	3 —OH (1, 3, 5)	218	subl.	120 weak
3. *Aromatic carboxylic acids*						
Benzoic acid	122	7	1 —COOH	122	249	80
Salicylic acid	138	7	1 —COOH, 1 —OH (1, 2)	159	subl.	85
p-Hydroxybenzoic acid	138	7	1 —COOH, 1 —OH (1, 4)	215	—	120
Gentisic acid	154	7	1 —COOH, 2 —OH (1, 2, 5)	205	—	120
Gallic acid	170	7	1 —COOH, 3 —OH (1, 3, 4, 5)	255	—	not extractable
4. *Pyrones*						
Coumarin	146	9	1 —O—, 1 Keto-Gp.	71	301	70 strong
Umbelliferone	162	9	1 —OH, 1 —O—, 1 Keto-Gp.	230	subl.	100
Aesculetin	178	9	2 —OH, 1 —O—, 1 Keto-Gp.	276	subl.	not extractable
5. *Lipids*						
Myristyl alcohol	214	14	1 —OH	39	263	70
Cholesterol	386	27	1 —OH	148	360	85
Triolein	885	57	3 —COOR	—	235	90

can be extracted with carbon dioxide in the lower pressure range alone. Consideration of the individual groups of substances, *e.g.* the aromatic hydrocarbons, phenols, aromatic carboxylic acids, pyrones, and lipids, is highly informative (Table 2). It is immediately evident that the extractability falls sharply in the pressure range up to 400 bar as the number of C-atoms increases and particularly following the introduction of polar functional groups. One can see here the possibilities for fractionating extraction of complex samples in a pressure gradient.

The findings obtained so far with model substances can be summarized under the following *rules of thumb*:

a) Hydrocarbons and other typically lipophilic organic compounds of relatively low polarity, e.g. esters, ethers, lactones, and epoxides, can be extracted in the lower pressure range, i.e. 70—100 bar.

b) The introduction of strongly polar functional groups (e.g. —OH, —COOH) makes the extraction more difficult. In the range of benzene derivatives, substances with three phenolic hydroxyls are still capable of extraction, as are compounds with one carboxyl and two hydroxyl groups. Substances in this range that cannot be extracted are those with one carboxyl and three or more hydroxyl groups.

c) More strongly polar substances, e.g. sugars and amino acids, cannot be extracted in the range up to 400 bar.

d) Fractionation occurs in the pressure gradient when there are greater differences in the commencement of boiling or sublimation, i.e. in the volatility, and/or marked differences in the polarity of the substances (DC value). The fractionation effects are most marked in the range where there is a sharp rise in the density and dielectric constant of fluid carbon dioxide (Fig. 1).

With these general rules it is now possible to estimate the extractability of the different substances.

3.2. Study of Complex Mixtures in the Pressure Range of up to 400 bar

3.2.1. Extraction of Lipophilic, Non-basic Substances

In continuation of the above fundamental studies we extracted a series of complex mixtures with supercritical gases.

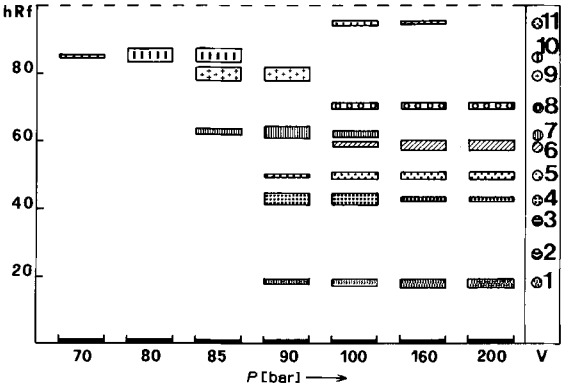


Fig. 5. FE-TLC of a mixture of eleven dyes extracted with carbon dioxide at 40 °C: 1) Fat Orange, 2) Indophenol, 3) Ceres Black, 4) Sudan Red, 5) Sudan Blue, 6) Ceres Red, 7) Ceres Orange, 8) Ceres Green, 9) Sudan Yellow G, 10) Sudan Yellow liquid, 11) Sudan Orange. The fractionating effect was assessed on the basis of the zone width. Plate coating: silica gel 60 F_{254}, dichloromethane, 1 × 15 cm, CS. Detection: observation in daylight.

The resulting fluid extraction thin-layer chromatograms (FE-TLC) provide immediate valuable information on extractability in the respective pressure ranges. They show the increase or decrease in the quantity and the fractionation effects that can be achieved. For example, in Figure 5—the FE-TLC of a mixture of eleven dyes—fractionation of several dyes in the pressure range of 70—100 bar is clearly visible.

The extraction of biological substances present in plant material provided basic confirmation of the results obtained with the model substances, although the fact that the substances are present in the plant material as salts, hydrogen-bonded, or even microencapsulated constitutes a disadvantage for the extraction process. It can be seen from Figure 6 that the terpene hydrocarbons were extracted from camomile flowers at about 70 bar, as were the sesquiterpene alcohol bisabolol and the coumarin herniarin.

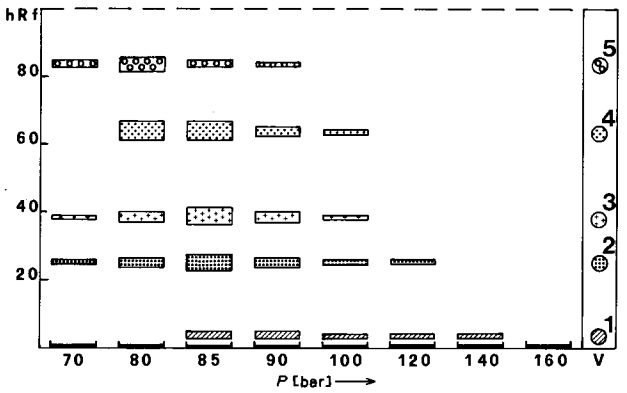


Fig. 6. FE-TLC of 50 mg of camomile flowers extracted with carbon dioxide at 40 °C. 1) matricin, 2) herniarin, 3) bisabolol, 4) "ene-yne dicycloethers", 5) terpene hydrocarbons. Plate coating: silica gel F_{254}, chloroform-benzene (75 + 25), 2 × 12 cm, CS. Detection: a) UV_{365} (herniarin, blue fluorescence); b) EP reagent [7], 10 min 110 °C (matricin, green-blue).

Extraction of the "ene-yne dicycloethers" begins at 80 bar, and the proazulene matricin is extracted at about 85 bar.

An example of the extraction of plant material containing fatty oils with supercritical carbon dioxide is provided by the FE-TLC of sunflower seed that was impregnated with 0.5 % of squalene (Fig. 7). The extraction of squalene begins

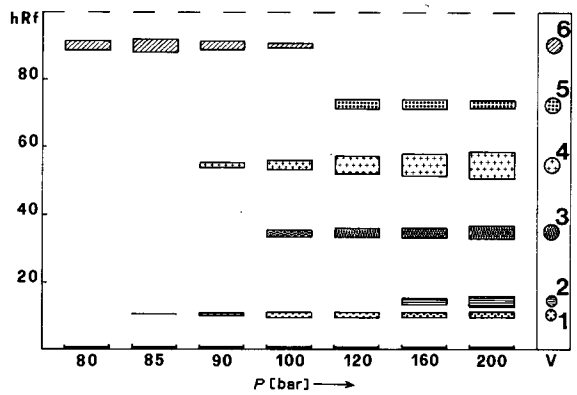


Fig. 7. FE-TLC of 80 mg of sunflower seeds (with 0.5 % of squalene added) extracted with carbon dioxide at 40 °C. 1) sterols, 2) diglycerides, 3) triglycerides with epoxy acids, 4) triglycerides, 5) steryl esters, 6) squalene. Plate coating: silica gel 60 F_{254}, petroleum ether (b. p. = 40—60 °C)—diethylether—acetic acid (70 + 30 + 1), 1 × 10 cm, CS. Detection: acetic anhydride-sulfuric acid reagent [7], heated for 10 min, then UV_{365} (fluorescence).

above 80 bar. At 85 bar the squalene zone is already strongly formed and a weak sterol zone can be seen for the first time. The triglycerides, the main constituents, appear above 90 bar; the triglyceride zone increases steadily with increasing pressure. Extraction of the steryl esters begins at 120 bar, and the diglycerides become visible on the FE-TLC above 160 bar. From a practical point of view, separation of the triglycerides from the other constituents would be possible only below 90 bar; this is also evident from other examples of plant material extraction (Table 3).

Table 3. Microextractions of plant material by the new coupled FE-TLC method.

Plant material air-dry	Principal constituents shown by TLC	Rel. molecular weight	Molecular formula	M.p. [°C]	B.p. [°C]	Extractable from [bar]
Caraway fruits	Limonene	136	$C_{10}H_{16}$	−74	178	70
	Carvone	150	$C_{10}H_{14}O$	—	231	70
	Triglycerides	>600	—	—	—	90
Peppermint leaves	Menthol	158	$C_{10}H_{20}O$	44	216	70
	Menthone	156	$C_{10}H_{18}O$	—	209	70
Camomile flowers	Herniarin	176	$C_{10}H_8O_3$	117	—	70
	α-Bisabolol	222	$C_{15}H_{26}O$	—	155	70
	"Ene-yne dicycloethers" [a]	200	$C_{13}H_{12}O_2$	—	—	80
	Matricin	306	$C_{17}H_{22}O_5$	—	—	85
Raw coffee	Caffeine	194	$C_8H_{10}N_4O_2$	178 subl.	—	80
	Triglycerides	>600	—	—	—	90
Marihuana (Cannabis)	Cannabidiol	314	$C_{21}H_{29}O_2$	66	—	85
	Cannabinol	310	$C_{21}H_{26}O_2$	76	—	90
	Tetrahydrocannabinol	315	$C_{21}H_{30}O_2$	76	—	90
Sunflower seeds	Squalene	410	$C_{30}H_{50}$	−20	280	80
	Cholesterol	386	$C_{27}H_{26}O$	148	360	85
	Triglycerides	600	—	—	—	90
Sesame seeds	Sesamin	354	$C_{20}H_{18}O_6$	123	—	85
	Triglycerides	>600	—	—	—	90

[a] The "ene-yne dicycloethers" are a mixture of *cis*- and *trans*-spiroethers.

3.2.2. Extraction of Alkaloids

Special attention was also paid to alkaloids and the plant material they are obtained from. These represent a fairly heterogeneous class of natural products as far as the relative molecular weight and polarity are concerned. Here again we found definite correlations between the extractability of alkaloids and their constitution. As shown by Table 4, in addition to carbon dioxide we tried nitrous oxide in these tests. For alkaloids with relatively polar functional groups, such as hydroxyl groups, supercritical carbon dioxide is a poor extractant; supercritical nitrous oxide yields much better results.

with carbon dioxide, fluid nitrous oxide is also the better extraction gas for relatively nonpolar alkaloids. Apart from the polarity of the alkaloids, their extractability is affected by their melting and boiling points. These correlations are also evident from Table 5, which lists some data on the fluid extraction of several alkaloids from plant material.

Here, however, salt formation, hydrogen bonding, and the diffusion effects necessary for extraction inhibit the course of the process.

That fluid nitrous oxide gives better extraction of alkaloids, particularly in the lower pressure range, could well be due

Table 4. Alkaloid model substances, extracted directly from quartz wool with supercritical carbon dioxide or nitrous oxide at 40°C. The polarity of the alkaloids increases from top to bottom within each group.

Alkaloid	Rel. molecular weight	Functional groups	M.p. [°C]	Commencement of FE [bar] CO_2	N_2O
1. Colchicine	399	4 —OCH_3, 1 —NHAc, 1 Keto-Gp.	155—157	100	80
2. *Ipecacuanha alkaloids*					
O-Methylpsychotrine	478	4 —OCH_3	123—124	80	80 strong
Emetine	480	4 —OCH_3, 1 —NH	74	200	80 good
Cephaeline	466	1 —OH, 3 —OCH_3, 1 —NH	120—130	—	80
Psychotrine	464	1 —OH, 3 —OCH_3	122	—	150
3. Nicotine	162	1 —NCH_3	− 79	80 very strong	80 very strong
4. *Opium alkaloids*					
Papaverine	339	4 —OCH_3	147	90	80 strong
Narcotine	353	3 —OCH_3, 3 —O—, 1 Keto-Gp.	176	90	80 strong
Thebaine	311	2 —OCH_3, 1 —O—	193	90	80 good
Codeine	299	1 —OH, 1 —OCH_3, 1 —O—	155	90	80
Morphine	285	2 —OH, 1 —O—	254—256	—	200 very weak
5. *Rauwolfia alkaloids*					
Reserpine	608	5 —OCH_3, 1 —CO_2CH_3, 1 —OCO	262—263	80	80
Yohimbine	354	1 —OH, 1 —CO_2CH_3	240—241	90	80
Ajmaline	326	2 —OH	205—207	—	80
6. *Tropa alkaloids*					
Scopolamine	305	1 CH_2OH, 1 Ester, 1-Epoxide-Gp.	36—37	80	80 good
Atropine	289	1 —CH_2OH, 1 Ester	118	90 good	80 strong
Tropanol	141	1 —OH	64	90 good	80 good
7. *Vinca alkaloids*					
Vincamine	354	1 —OH, 1 —CO_2CH_3	232—232	90	80
Vinblastine	810	2 —OH, 1 —CH_3	210—211	80	120
Vincristine	824	2 —OH, 1 —CHO	218—220	80	150

The lower the polarity of an alkaloid, the lower the pressure that must be used for the extraction to begin. Compared

Table 5. Fluid extraction of alkaloid drugs with supercritical carbon dioxide or nitrous oxide at 40°C.

Plant material	Alkaloids revealed by TLC	Commencement of FE [bar] CO_2	N_2O
1. Nicotianae folium	Nicotine	90	80
2. Ipecacuanhae radix	*O*-Methylpsychotrine	—	120
	Emetine	200	80 good
	Cephaeline	—	90
	Psychotrine	—	120
3. Opium crudum	Papaverine	100	80 strong
	Narcotine	120	80 strong
	Thebaine	120	80 good
	Codeine	200	80
	Morphine	—	200 very weak
4. Rauwolfiae radix	Reserpine	80	80
	Ajmaline	—	80

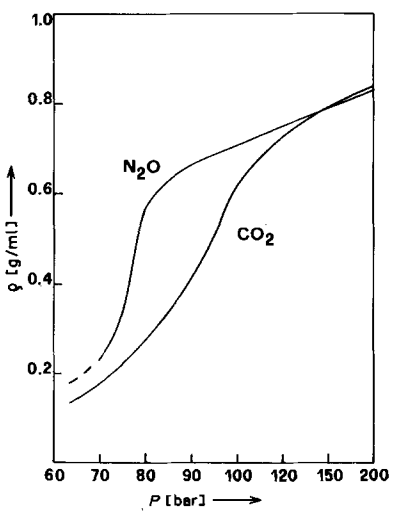


Fig. 8. Pressure dependences of the densities of supercritical carbon dioxide and nitrous oxide at 40°C.

to the fact that under these conditions nitrous oxide has a higher density than carbon dioxide (Fig. 8).

Compared with fluid carbon dioxide, it is better able to solvate the alkaloids in the fluid extraction process. Furthermore, unlike nitrous oxide, carbon dioxide is known to have no dipole moment, and therefore cannot interact with polar groups in the alkaloids. The basic character of the alkaloids does not appear to have any marked influence on their extractability with fluid carbon dioxide and nitrous oxide. Alkaloids with roughly the same basicity, such as morphine and codeine, are extracted to different degrees because of their different polarity. The behavior of the neutral colchicine also shows that the basicity is of minor importance where extraction is concerned.

A vivid example of the possibilities of fluid extraction is provided by the FE-TLC of opium. The plant material was extracted in this instance with supercritical nitrous oxide at 40°C. It is evident from the extent of the individual zones (Fig. 9) that the alkaloids papaverine and narcotine are extracted particularly easily. These are followed by thebaine, which exhibits good extractability at only about 120 bar. The extraction of codeine is less good and that of morphine is worst. In view of the new trend of extracting thebaine from *Papaver bracteatum*, the results of the fluid extraction are of particular interest.

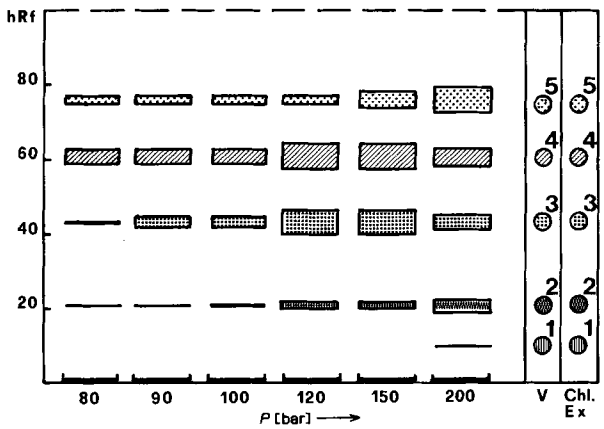


Fig. 9. FE-TLC of 100 mg of crude opium extracted with nitrous oxide at 40°C. 1) Morphine, 2) codeine, 3) thebaine, 4) papaverine, 5) narcotine. Plate coating: silica gel 60 F_{254}, toluene-acetone-ethanol-2.5% ammonia solution (45 + 45 + 7 + 3), 1 × 10 cm, CS. Detection: Dragendorff reagent, modified after *Puech* [8], dark-brown zones.

If supercritical carbon dioxide is used, on the other hand, codeine and morphine are not extracted at all until at least 200 bar. The other three alkaloids are also far less soluble. Further details about the extractability of alkaloids from areca, china, colchicum, conium, ephedra, ipecacuanha, nicotiana, rauwolfia, tropa, and vinca are given in the original paper[9].

4. Quantitative Study of the Solubility Behavior of Model Substances in Supercritical Gases

Exact determination of the solubility of selected substances as a function of pressure is important for further development of the general rules based on the qualitative tests. In addition, knowledge of the solubility of the substances to be extracted is required if the yields of plant material extraction processes with supercritical gases are to be calculated.

Figure 10 shows the relationship between solubility and pressure for three aromatic carboxylic acids and for 1,8-dihydroxyanthraquinone between 80 and 200 bar. Benzoic acid, the most lipophilic compound of this group, can be detected qualitatively already below 70 bar.

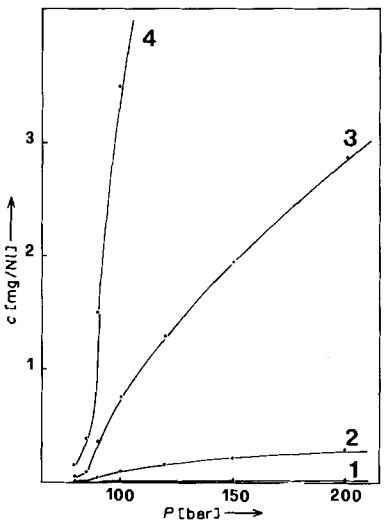


Fig. 10. Pressure dependences of the solubility of a number of solids in supercritical carbon dioxide at 40°C. 1) *p*-Hydroxybenzoic acid, 2) 1,8-dihydroxyanthraquinone, 3) salicylic acid, 4) benzoic acid.

The concentration in the gas does not rise very markedly until the level of 85 bar has been reached; at 100 bar it is about 3.5 mg/Nl, while at 150 bar it is already about 9 mg/Nl. This represents a 10^4- to 10^5-fold increase over the quantity expected solely on the basis of the vapor pressure calculated from the ideal gas equation.

The slope of the solubility curve declines again between 90 and 100 bar with increasing pressure. Salicylic acid, which is rather more polar because of the OH-group *ortho* to the carboxyl group, has a lower solubility. Its concentration in the gas at 150 bar is 2 mg/Nl. If, on the other hand, the hydroxyl group is *para* to the carboxyl group, as in *p*-hydroxybenzoic acid, the solubility is strongly reduced, namely to only about ~10 μg/Nl at 150 bar.

5. Extractability of Polar Natural Products in the Range of up to 2500 bar

Giddings et al. succeeded in dissolving and chromatographing sugars and amino acids, among other substances, with supercritical carbon dioxide at high pressures, *i.e.* above 100 bar in this context[10]. On the basis of model calculations with modified Hildebrand's solubility parameter, these authors concluded that supercritical carbon dioxide and isopropanol have comparable dissolving power at comparable density. To assess the extractability of polar natural products at pressures in excess of 2000 bar we carried out quantitative solubility determinations in this pressure range with supercritical carbon dioxide and nitrous oxide[11]. We found the solubility of amino acids, sugars, and other polar natural products in supercritical carbon dioxide at over 2000 bar to be less than 10 μg/Nl,

i.e. $< 1 : 200000$. These substances are at least 500 times more soluble in isopropanol.

The pressure-dependent solubility of various substances in supercritical gases at 40 °C is shown in Figure 11. The anthraquinone glycoside frangulin A was extracted with supercritical carbon dioxide and supercritical nitrous oxide, while the corresponding aglycone, emodin, was extracted with supercritical carbon dioxide.

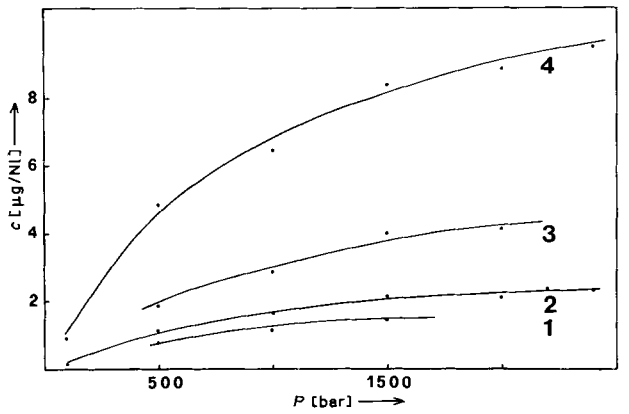


Fig. 11. Pressure dependence of the solubility of a number of substances in supercritical gases at 40 °C. 1) Frangulin A in nitrous oxide, 2) frangulin A in carbon dioxide, 3) aesculetin in carbon dioxide, 4) emodin in carbon dioxide.

These two substances differ considerably in polarity and, as was to be expected, their solubility curves were different; the more strongly polar frangulin A is less soluble than emodin. Both solubility curves have the same characteristics as the curves for sugars, amino acids, and even for example the more soluble *p*-hydroxybenzoic acid; the solubility of the latter at 2000 bar is about 40 µg/Nl.

Frangulin A is about 35 % less soluble in supercritical nitrous oxide than in carbon dioxide under the same conditions. Generally, the higher the polarity (and the lower the volatility) of the substances, the flatter are the curves. A number of polar natural products that could not be extracted and detected with the direct FE-TLC coupling with supercritical carbon dioxide up to 400 bar were also investigated. Only the solubility of aesculetin (cf. also Table 2) could be determined quantitatively (Fig. 11). On the other hand, the solubility of gallic acid and 2,6-dihydroxyanthraquinone, for example, was so low in supercritical carbon dioxide even at 2500 bar that the quantities extracted were insufficient for quantitative determination. The concentrations in compressed carbon dioxide were below 0.1 µg/Nl.

All the solid natural products tested exhibit the same characteristic sigmoid form of the solubility curve in the lower pressure range above 80 bar. The turning point is at about 90 bar; as the pressure increases, the slope becomes less steep. This course of the curve continues for all the substances tested until over 2000 bar. On the whole, the solubility curves resemble the density isotherms at 40 °C in their pressure dependence (cf. Fig. 1). This dependence of the solubility on the density of the gas is probably due to the fact that at higher densities more particles are available for solvation. As the density increases so too does the polarity (DC value), which is frequently cited for the solubility. The relationship is explained by the Clausius-Mosotti equation[12]. However, there is no linear relationship between the gas density and the dissolving power. If the logarithm of the substance concentration (for a wide variety of substances) in the compressed gas is plotted against the logarithm of the gas density, a direct proportionality is found in a pressure range of roughly 80 bar to 2000 bar (and higher). A few examples are shown in Figure 12.

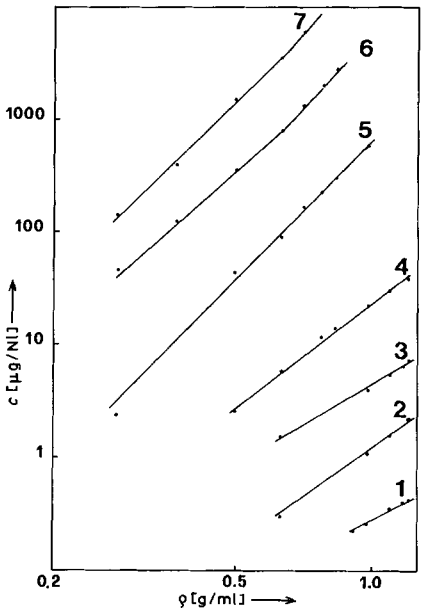


Fig. 12. Dependence of the solubility of a number of substances in carbon dioxide at 40 °C on the (pressure-dependent) density of the carbon dioxide. 1) Glycine, 2) frangulin, 3) emodin, 4) *p*-hydroxybenzoic acid, 5) 1,8-dihydroxyanthraquinone, 6) salicylic acid, 7) benzoic acid.

The solubility curves can be described by the simple straight-line equation:

$$\ln c = m \times \ln \rho + \text{const.}$$

The constants and the factor m contain characteristic quantities of the substance properties. The solubility of polar substances in supercritical carbon dioxide and nitrous oxide has proved to be so low that the expenditure necessary for an industrial extraction plant working at up to 2000 bar and higher cannot be justified. The situation is still less favorable in the case of extraction from plant material.

6. Discussion of the Results and Future Prospects

Summarizing the experience gained with our microscale methods for practical application, it can be said that fluid extraction with carbon dioxide will be largely restricted to lipophilic natural products. It is of particular interest that the gas densities are easily variable between 0.2 and 0.9 g/ml in the lower pressure range slightly above the critical temperature. This easily effected fourfold increase in density results in a sharp enhancement of the dissolving power and can be achieved in the region of the critical temperature by relatively small increases in pressure. Furthermore, by the reverse process it is also possible to achieve fractionating separation and hence a further concentration of specific substances. We made use of this effect, for example, to obtain camomile extracts

with a high concentration of matricin[13]. In order to evaluate extraction tests it will be particularly important to determine the solubilities quantitatively, and this too is possible with our method. In our view, solubilities of at least 1:500 to 1:1000 are needed if the fluid extraction process is to be applied on a technical scale.

A further problem that will continually arise is the presence of the material in complex samples. In this respect extractability can be hindered even mechanically by a type of microencapsulation. Furthermore, salts or strong hydrogen bonds may also be present. Some of these obstacles may be eliminated by suitable additives to the material for extraction. In this connection we are thinking, for example, of moistening the material and, if necessary, of adding ammonia. Also worth investigating is the influence of auxiliaries which, when mixed with the extraction gas, increase the dissolving power, *i.e.* improve the extractability. Greater attention will also be paid in future to competitive phenomena such as occur, for example, when the plant material is moistened. With the microextraction methods at our disposal it is relatively simple to investigate the extraction properties of other supercritical gases, ethylene and certain freons undoubtedly being of prime interest in this context.

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New analytical methods (13)

Chromatography with Supercritical Fluids

By E. Klesper[*]

Chromatography with supercritical fluids unites the features of both gas chromatography and liquid chromatography, yet retains special characteristics of its own. The diffusion coefficient and particularly the viscosity of fluid phases may approach values for low-pressure gases, while the solvent power may be similar to that of liquids. However, with supercritical fluids it is possible to control chromatographic separations very effectively by pressure programming, since the solubility increases with increasing density. Temperature programming, on the other hand, can have the opposite effect to that in gas- or liquid-chromatography since the density decreases with increasing temperature at a given pressure. Supercritical fluid chromatography is primarily of interest for the separation of higher molecular weight compounds. The efficiency of this method of separation is demonstrated on several homologous series. Thus, a styrene oligomer with nominal $M_w = 2200$ can be resolved by a pressure and temperature program into 40 species.

1. Introduction

Substances of higher molecular weight do not have sufficiently high a vapor pressure to be able to be chromatographed with low-pressure gases as the mobile phase. However, if the gas pressure is increased considerably, *e.g.* to within the range of the critical pressure the mobile phase may assume sufficient "solvent power" to induce migration of even very high molecular weight substances on chromatographic columns. The temperature of the system is so chosen as to avoid liquefaction at a given pressure, *i.e.* it is generally kept above the critical temperature. The permanent gases frequently employed in gas chromatography, such as N_2, He, and Ar, develop only moderate "solvent power" at elevated pressures. Low-boiling solvents, however, including for instance CO_2, pentane, and isopropanol, which are thermally stable and unreactive with substrate and stationary phase, may be suitable solvents in the fluid state.

The "solvent power", of dense gases, particularly of solvents above their critical temperature, has long been recognized[1, 2] and has been reviewed on a number of occasions[3, 4]. Compressed gases, however, have been utilized only relatively recently for chromatographic separations[5–8], as in fact they have been for extraction purposes, or as reaction media.

Previous work in supercritical fluid chromatography has been carried out with low-boiling solvents above their critical temperature[9, 10], as well as with permanent gases[11, 12]. As a substrate, a wide variety of low vapor pressure compounds

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have been studied, *e.g.* polycyclic arenes[13], higher *n*-alkanes[6], phthalates[14], cyclopentadienylmetal complexes[15], pentanedionatometal complexes[16], and numerous substances of biochemical interest, including *e.g.* porphyrins[17], sugars, amino acids and proteins[9]. In addition, oligosiloxanes[18] and oligostyrenes[19-21] have also been investigated.

Different modes of chromatographic separation have been reported, namely fluid-solid[13], fluid-liquid[14], and chromatography on gels[22]; a reprecipitation-redissolution mode of separation has also been proposed[20, 23]. Several apparatus for fluid chromatography have been described, relatively simple designs at first[5, 6], followed by devices of higher capabilities[8, 9, 14, 24, 25], including those which allow temperature and pressure programming[18, 23, 26]. Detectors suitable for supercritical fluid chromatography have also been a matter of important concern[27].

The basic principles of supercritical fluid chromatography have been investigated by several groups. Thus, solubilization in compressed gases has been studied and discussed[9, 28, 29] and a series of pertinent phase diagrams have been determined[30-34]. Other investigations have been concerned with pressure induced equilibrium shifts[35], nonideality in dense gases[12], capacity ratios[6, 36], and modified van Deemter equations applied to supercritical fluid chromatography[28, 37, 38].

2. Supercritical Fluids

Table 1 lists some of the low-boiling substances which may be expected, in their supercritical dense state, to dissolve specific classes of compounds, including those of relatively high molecular weight[10, 26]. Others may be added[9], and still others may be considered, such as dimethylether, trimethylamine and tetrahydrofuran.

Table 1. Properties of some compounds which may be suitable for chromatography with supercritical fluid phases.

	B.p. [°C] at 1 atm	Critical data T_c [°C]	P_c [atm]	ρ_c [g/cm³]
CO_2	−78.5	31.3	72.9	0.448
NH_3	−33.4	132.3	111.3	0.24
H_2O	100	374.4	226.8	0.344
Methanol	64.7	240.5	78.9	0.272
Ethanol	78.4	243.4	63.0	0.276
Isopropanol	82.5	235.3	47.0	0.273
Ethane	−88	32.4	48.3	0.203
n-Propane	−44.5	96.8	42.0	0.220
n-Butane	− 0.5	152.0	37.5	0.228
n-Pentane	36.3	196.6	33.3	0.232
n-Hexane	69.0	234.2	29.6	0.234
2,3-Dimethylbutane	58.0	226.8	31.0	0.241
Benzene	80.1	288.9	48.3	0.302
Dichlorodifluoromethane	−29.8	111.7	39.4	0.558
Dichlorofluoromethane	8.9	178.5	51.0	0.522
Trichlorofluoromethane	23.7	196.6	41.7	0.554
1,2-Dichlorotetrafluoroethane	3.5	146.1	35.5	0.582
Chlorotrifluoromethane	−81.4	28.8	39.0	0.58
Nitrous oxide	−89	36.5	71.4	0.457
Diethyl ether	34.6	193.6	36.3	0.267
Ethyl methyl ether	7.6	164.7	43.4	0.272

As an approximation, the solvent power of a solvent may be assessed by the solubility parameter $\delta = \sqrt{\Delta H/V}$, where ΔH is the heat of vaporization and V the molar volume[39]. Proceeding to a supercritical dense gas, the solubility parameter may be written

$$\delta = 1.25\, P_c^{0.5}(\rho_{r,g}/\rho_{r,l}) \quad (1)$$

where P_c is the critical pressure, $\rho_{r,g}$ the reduced density of the gas, and $\rho_{r,l}$ the reduced density of the liquid of a given mobile phase[7, 39]. If it is presupposed that the solubility parameters of the fluid and the solute should be about equal for good solubility, one may estimate which supercritical dense gas and which density $\rho_{r,g}$ would be suitable for a given substrate. However, the usual qualifications[7, 39] for the validity of the solubility parameter concept will probably also apply for dense gases. In particular, specific solvent effects for polar and hydrogen bonding solvents can be of considerable importance.

An increase in the density of the supercritical mobile phase results in a higher solubility parameter; higher δ values are usually needed for substances of high molecular weight. However, it is the lower density of the supercritical fluids as mobile phase, compared with the density of liquids below their boiling points, which forms the basis for a potentially higher chromatographic efficiency of fluids. This prediction is supported by the typical properties of low-pressure gases, liquids and supercritical fluids[10] given in Table 2.

Table 2. Physical properties of gases, liquids, and supercritical fluids [10].

Property	Symbol	Units	Gas	Liquid	Supercritical fluid phase
Density	ρ	[g/cm³]	10^{-3}	1	0.3
Diffusivity	D	[cm²/s]	10^{-1}	5×10^{-6}	10^{-3}
Dynamic viscosity	η	[g cm^{-1} s^{-1}]	10^{-4}	10^{-2}	10^{-4}

The data are only approximate, but they demonstrate that the diffusivity of a fluid is between that of a gas and a liquid, while the viscosity more closely approximates that of a gas. Since the diffusivity and viscosity, as well as the packing geometry, govern the radial mass transport of the mobile phase in columns, correspondingly small theoretical plate heights (HETP) should be attainable. It is assumed, of course, that the diffusivity of the substrate shows almost similar behavior to that of the fluid. The low viscosity with increasing density also leads to higher Reynolds numbers $R_{e,p} = (d_p \bar{v} \rho)/\eta$ than in the case of liquids. The Reynolds number $R_{e,p}$ is related to the particle size d_p, $\bar{v}$ is the average linear velocity of the mobile phase, ρ the density and η the dynamic viscosity[38]. In the case of fluids the ratio ρ/η may exceed 10^3 s cm^{-2}, while in the case of liquids and gases it is one and two orders of magnitude lower, respectively. Reynolds numbers above 10 lead to turbulence in packed beds, increasing further the radial mass transport and relaxing flow profiles.

It should be pointed out that it is not actually the density of a fluid which is intimately connected to dissolution power, viscosity, and diffusivity, but the free volume of the fluid,

combined with molecular geometry and specific interactions between fluid and substrate. It appears that the free volume should be kept as high as is compatible with the necessary dissolution power. Besides the solubility and free volume, the temperature is also of importance in fluid chromatography, since the decomposition temperature of the substrate may not be exceeded. Also, an operating temperature well above the critical temperature might be of advantage; the isotherms in the pressure-density diagram (Fig. 1) show very high compressibilities near the critical temperature, indicating a similarity to the liquid state. Raising the temperature will decrease η and increase D. Furthermore, an operative advantage is lost in this region of high compressibility, since a pressure programming, aimed at a steady and increasingly slower rise in density, is made difficult.

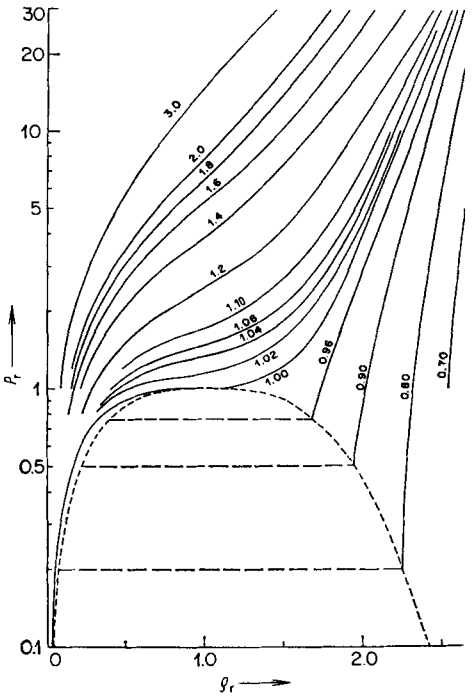


Fig. 1. Plot of reduced pressure P_r *versus* reduced density ρ_r, with reduced temperature T_r as parameter. Two phase region bordered by dashed curve (after [7]).

3. Instrumentation

An obstacle to the development of supercritical fluid chromatography was the lack of an apparatus allowing independent control and programming of the instrumental parameters for the separation, *i.e.* pressure, temperature, flow rate, and composition of the mobile phase. Furthermore, a detector was required which could operate at elevated pressures and which, if possible, was also insensitive to pressure changes. The latter is particularly important with pressure programming. The apparatus shown in Fig. 2 has been constructed bearing these objectives in mind[120, 23]. The characteristic design feature is a pressure cascade of three levels. Each pressure level is controlled by an electronic feedback loop system.

The feedback loop (13) (see Fig. 2) allows the programming of pressure for the chromatographic column (6) while the column oven (4) may be simultaneously and independently temperature programmed with (11). During any pressure and temperature changes for the column, the feedback loop (12)

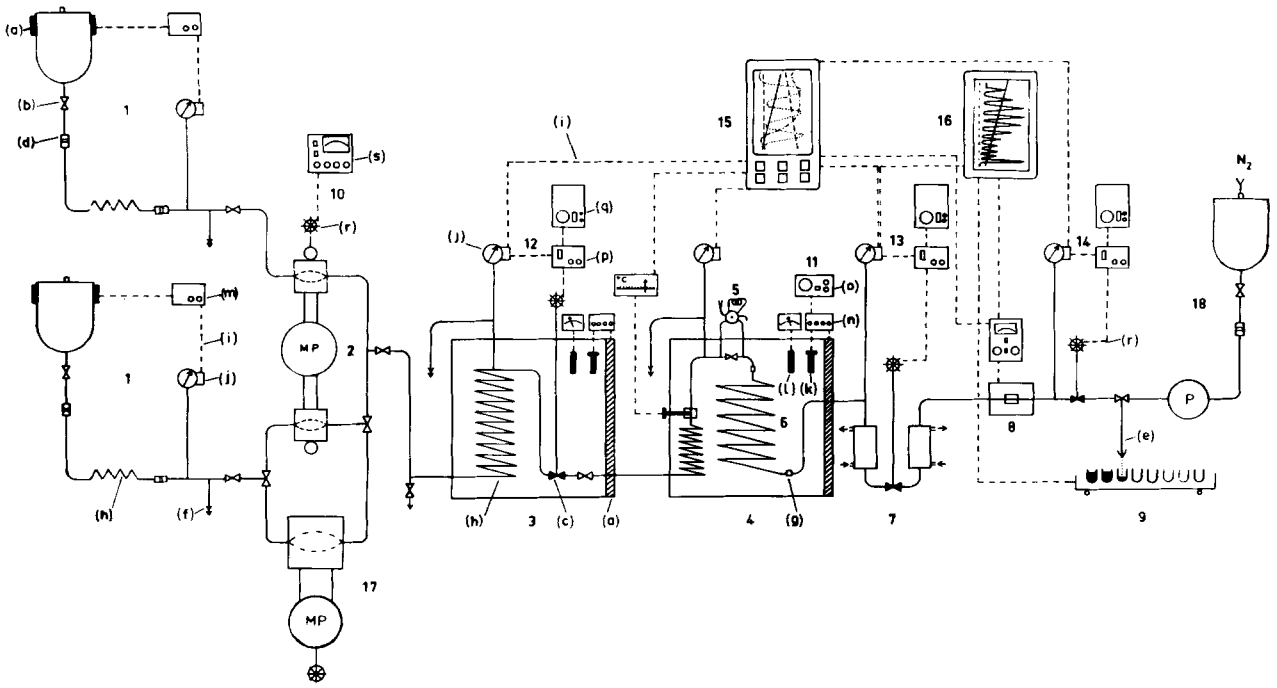


Fig. 2. Supercritical fluid chromatograph. Sections of the apparatus which are marked by numerals are explained in the text. Key to symbols: (a) heating element; (b) shut off valve; (c) metering valve; (d) sintered metal filter; (e) exit; (f) exit with safety head containing a burst disc; (g) column connection; (h) coil of tubing; (i) electrical connection; (j) manometer device; (k) thermoelement; (l) mechanical mercury manometer; (m) relay for heating current; (n) temperature controller; (o) temperature programmer; (p) controller of feedback loop; (q) programmer of feed back loop; (r) stepping motor for controlling either the feed rate of a pump or driving the shaft of a metering valve; (s) programmer for feed rate.

keeps the pressure of the supply unit (1, 2, 3) at a constant and higher level, easing programming of feed rate and of composition of the mobile phase (10). In the supply unit, a double-headed membrane pump (2), capable of 500 bar, allows solvents to be fed from two tanks (1) simultaneously and to enter the oven (3) together. In oven (3) a constant supercritical temperature is maintained; pulsations are smoothed out by the buffering volume of a large diameter coil. An extra pump (17) allows pressures of up to 3000 bar to be reached.

The supercritical mobile phase from oven (3) enters oven (4) and first passes through a temperature conditioning coil and a sample injection device (5) before entering the chromatographic column (6). The eluate from the column is liquified again by passage through two heat exchangers (7), then passes through the UV-detector (8) and, in cases when the boiling point of the mobile phase is below room temperature, is taken up by an auxiliary solvent system (18) before finally being collected in the fraction collector (9). The detector unit (7, 8) is kept at a constant pressure by the feedback loop (14), the pressure being kept sufficiently high to exceed the vapor pressure of the now liquid mobile phase at room temperature. The detector recordings and column pressure recordings are traced out by recorder (16), while those of the temperature of the column oven (4) and the mobile phase itself, as well as those of other operating parameters, are monitored by recorder (15).

4. Separations

With the chromatograph described in Section 3, oligostyrenes *(1)* prepared by anionic initiators and having an average molecular weight $\bar{M}_w = 900$ were separated on porous silica with 90% *n*-pentane/10% methanol (v/v) as mobile phase. The chromatogram obtained is shown in Figure 3.

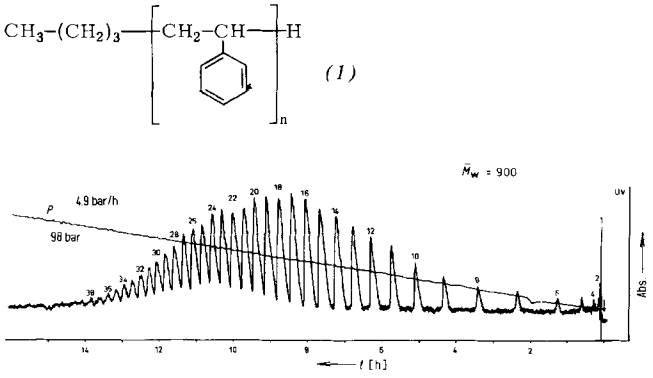


Fig. 3. Chromatogram of styrene oligomer (1) of nominal $\bar{M}_w = 900$. Mobile phase is 90% *n*-pentane and 10% methanol (v/v), feed rate: 1.9 ml/min (NTP), stationary phase: Porasil A (porous silica, Water Associates) particle diameter: 37—75 µm, pore size: < 100 Å. Sample size: 20 mg in 100 µl cyclohexane solution. $T = 235$ °C. The number of peaks corresponds to the degree of oligomerization (after [23]).

The time of sample injection is marked by an arrow. The sloping line *P* represents the column exit pressure, which is programmed with the feedback loop at the column exit [(13) in Fig. 2]. The pressure rises linearly at a rate of 4.9 bar/h, starting at 25 bar and reaching 98 bar after 15 h. The temperature is kept constant at 235 °C, well above the estimated critical temperature of the mixture [T_c(mixture) ≈ 207 °C; T_c(pentane) = 196.6 °C; T_c(methanol) = 240 °C]. The pressure drop of $\Delta P = 300$ bar over the 2 mm-ID column is considerable, due to the small particle size of the packing. As shown in Figure 3 the oligomeric species up to a degree of oligomerization of $n = 38$ were separated. With an oligostyrene of $\bar{M}_w = 2200$, peaks up to $n = 50$ could even be resolved. A smooth increase in pressure during the chromatographic runs is, however, essential for good resolution.

Without any increase in pressure—whether continuous or in steps—only a part of the oligomers may be eluted and resolved[23]. Even changing the speed of the pressure program affects the separation profoundly, as is demonstrated in Figure 4.

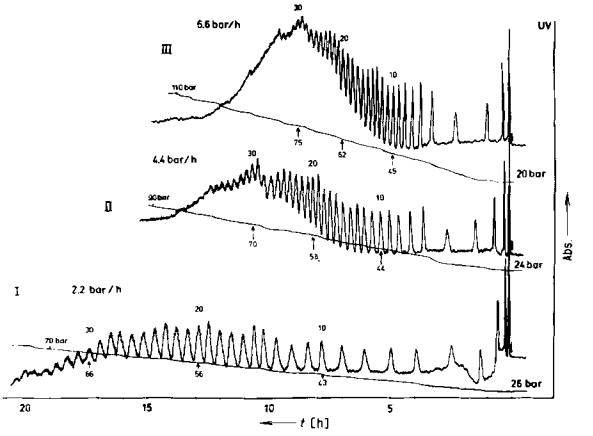


Fig. 4. Chromatograms of styrene oligomer *(1)* of nominal $\bar{M}_w = 2200$. Linear pressure program with differing rates of increase in pressure. Pressure drop over column: 25 bar. Mobile phase: 95% *n*-pentane/5% methanol (v/v), stationary phase: Porasil A, sample size: 40 mg in 100 µl cyclohexane solution, column: 6 m × 3 mm, $T = 220$ °C. Trace III: 6.6 bar/h increase, 2.6 ml/min; trace II: 4.4 bar/h increase, 3.0 ml/min; trace I: 2.2 bar/h increase, 3.2 ml/min. The number of peaks corresponds to the degree of oligomerization. The numbers below the arrows indicate the elution pressure for peaks 10, 20 and 30 (after [23]).

Increasing the pressure at a rate of 6.6 bar/h leads to far inferior resolution than when the increase in pressure is programmed at 2.2 bar/h, while at 4.4 bar/h an intermediate resolution is achieved. Naturally, improved resolution is coupled with a decrease in unresolved "background". A similar effect on pressure programming has also been observed with oligosiloxanes[18]. Comparing the pressures (Fig. 4) at which the same peak is eluted, and noting that the flow rates do not differ greatly, it would appear that the elution pressure is more important than elution volume. For comparison the elution pressures for peaks 10, 20, and 30 have been marked on the curves of the pressure programs. An analogous result is obtained when the pressure program is kept unchanged and the flow rate is varied. Elution pressure determines elution time more than elution volume.

Besides pressure, the temperature also has a major influence on the separation of the styrene oligomers on porous silica with *n*-pentane/methanol. From Figure 5 it can be seen that the resolution decreases rapidly with decreasing temperature as soon the temperature falls below T_c.

The pressures, even at the start of the chromatograms, are high enough to maintain the mobile phase in the liquid, rather than in the vapor state. If, however, temperatures

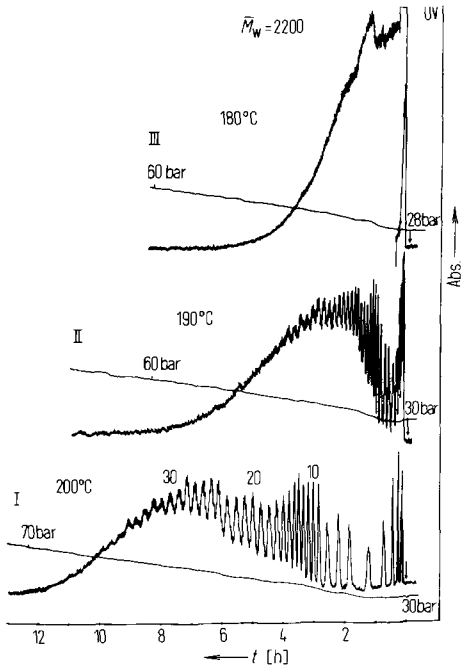


Fig. 5. Chromatograms at different temperatures below or near T_{cr}: at 180, 190 and 200°C. Similar pressure programs with 3.3 bar/h increase. Mobile phase: 95% *n*-pentane, 5% methanol, flow rates: 2.8 ml/min (trace III) 3.0 ml/min (trace II), and 2.8 ml/min (trace I): Other conditions as in Fig. 4 (after [23]).

approach T_c and then are raised above T_c, the resolution increases progressively, as shown in Figure 6. It may be concluded, therefore, that for best resolution the operating temperature should well exceed the critical temperature.

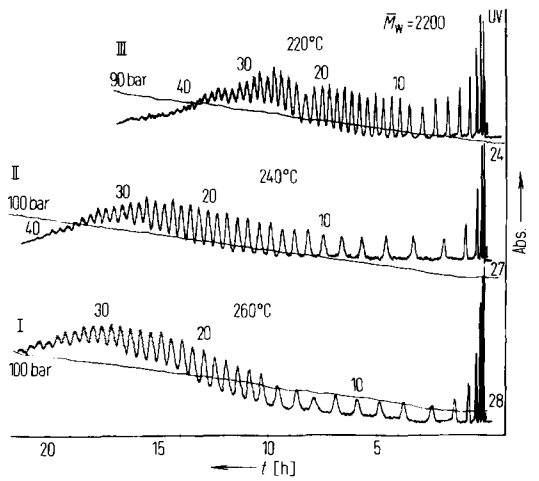


Fig. 6. Chromatograms at different temperatures above T_c: at 220, 240 and 260°C. Pressure program as in Fig. 5. Mobile phase: 95% *n*-pentane, 5% methanol. Flow rates: 2.75 ml/min (trace III), 3.0 ml/min (trace II) and 3.3 ml/min (trace I). Other conditions as in Fig. 4 (after [23]).

Since, for higher degrees of oligomerization, better resolution with simultaneous disappearance of unresolved background is desirable, a temperature program has been carried out simultaneously with the normal pressure program. For the chromatogram in Figure 7 the temperature first reaches 220°C only after 13 peaks have been eluted, thus reserving the higher temperatures up to 260°C for the higher oligomeric species. The resolution of the latter peaks appears to be better than in isothermal chromatograms. An increase in temperature at constant pressure reduces the density. This may lead to a slower increase in solubility with a given pressure program.

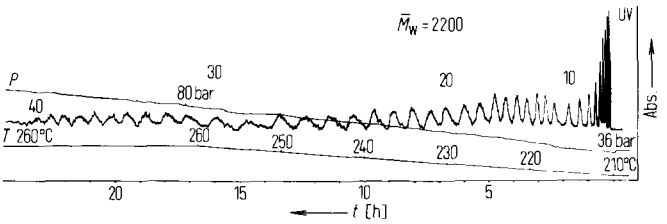


Fig. 7. Chromatogram with combined pressure and temperature program. Mobile phase: 95% *n*-pentane, 5% methanol at a flow rate of 4.2 ml/min. Pressure program starting at 36 bar and increasing linearly with 2.2 bar/h. Temperature program starting at 210°C and increasing linearly with 3°C/h up to 260°C. Other conditions as in Fig. 4 (after [23]).

A change in the composition of the mobile phase, by varying the amount of methanol, also has a large influence on the separation. Pure *n*-pentane without methanol shows smaller retention times and inferior resolution than *n*-pentane with 5% methanol (Fig. 8). It can be concluded, therefore, that adsorption on silica gel is not the dominant mechanism of this separation, for retention times should be decreased on addition of methanol on account of competitive adsorption and non-solubility of oligostyrenes in the methanol which is adsorbed on the surface. On using 10% methanol, the retention times are further increased, possibly because of the decrease in solubility power of the mobile phase. Consideration of this result, together with the fact there is always a pressure drop over the column, would suggest the mechanism of separation to be a reprecipitation-redissolution process for the zones of substrates migrating down the column. The pressure drop and the low initial pressure at the column exit lead to precipitation of the injected oligostyrenes. The pressure program then slowly raises the solubility, moving different oligomeric species by continuous reprecipitation-redissolution with different speeds down the column. In this connection, the experimental finding of a rather sharp threshold pressure of solubility for numerous substances is of interest, *i.e.* on exceeding a certain

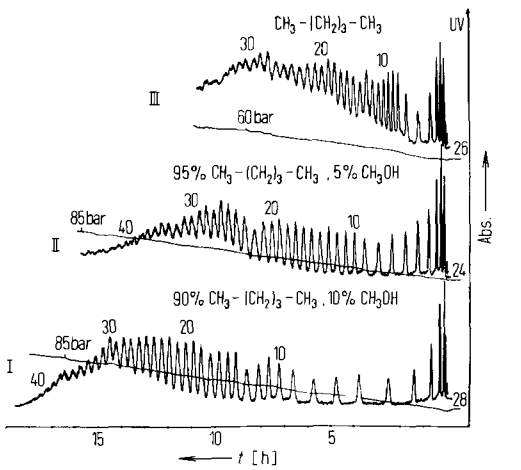


Fig. 8. Chromatograms, with variation of the methanol content of the mobile phase. Rate of pressure increase 3.3 bar/h. Trace III: 100% *n*-pentane, 3.1 ml/min; trace II: 95% *n*-pentane/5% methanol, 2.75 ml/min; trace I: 90% *n*-pentane/10% methanol, 3.1 ml/min. Other conditions as in Fig. 4 (after [23].

pressure, the substances become soluble in the supercritical phase[9]. This type of behavior is also reflected in the capacity ratios k' of columns which probably function by fluid-liquid partition[34]. The capacity ratio is defined by

$$k' = \frac{c''}{c'} \cdot \frac{V''}{V'} = K \cdot \frac{V''}{V'} \qquad (2)$$

where c'' and c' are the concentrations of substrate in the stationary ('') and the mobile phase ('), V'', V' the volumes of these phases and K the partition coefficient. The data for 4 higher molecular weight hydrocarbons are shown in Figure 9[36].

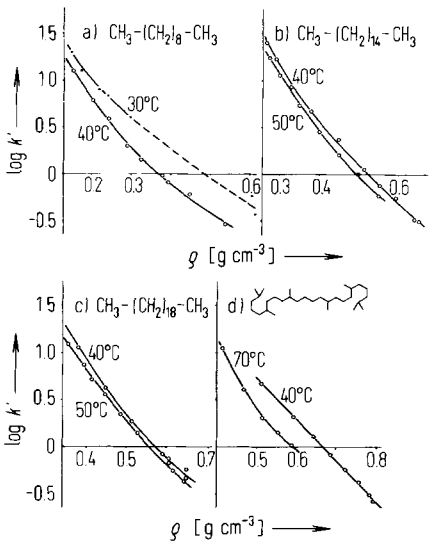


Fig. 9. Density and temperature dependence of capacity ratio k' for hydrocarbons in CO_2. Stationary phase: chemically bonded Carbowax 400 on silica gel (Durapak, 100—200 mesh, Waters Associates). Column dimensions: 2 m × 1.4 mm ID, flow rate: 0.5 $dm^3\,min^{-1}$ (NTP), sample size: 0.2 mm^3, no pressure program (after [36]).

Changing the density of the supercritical CO_2 by 0.01 g/cm^3, *i.e.* by changing the pressure by only about 2 bar, alters the capacity ratio k' by up to one order of magnitude. Hence, a relatively small increase in pressure, if in a critical range, will suffice to start movement of a substrate zone on a chromatographic column.

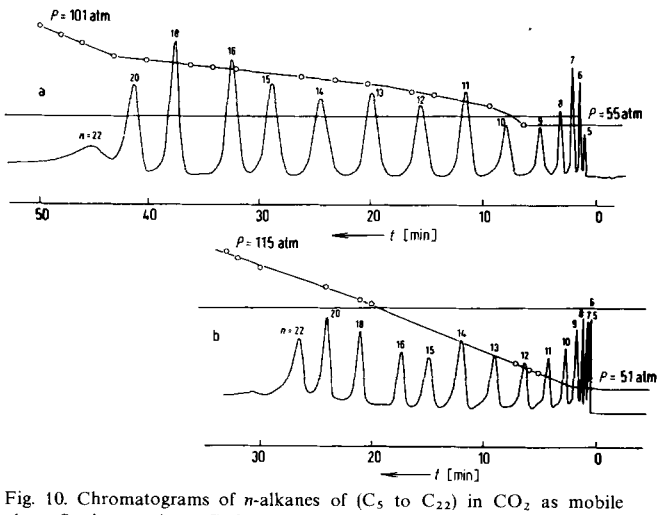


Fig. 10. Chromatograms of *n*-alkanes of (C_5 to C_{22}) in CO_2 as mobile phase. Stationary phase: Carbowax 400 bonded on porous silica gel (Porasil C). a) 40 °C, 1 l/min (NTP), slow pressure program; (b) 50 °C, 2 l/min (NTP), fast pressure program. Column: 3 m × 1.7 mm I D (after [28]).

A number of other homologous series, besides oligostyrenes, have been used as test cases for studying resolution in supercritical fluid chromatography. Figure 10 shows two chromatograms of a series of *n*-alkanes from C_5 up to C_{22} with CO_2 as the mobile phase and pressure programming. The homologous species are well separated, even with increased flow and enhanced rate of increase of pressure (Fig. 10b). Satisfactory separations have also been achieved without a pressure program, *e.g.* with a homologous series of di-*n*-alkyl phthalates[14] using isopropanol as the mobile phase (Fig. 11). If

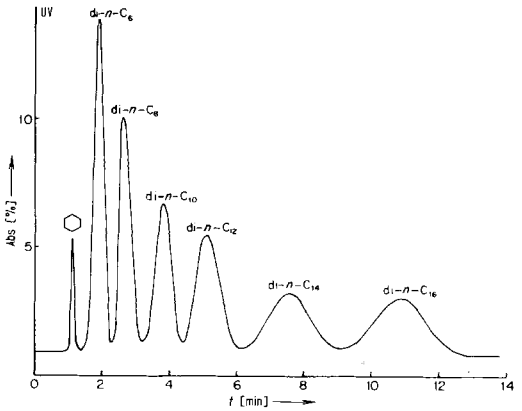


Fig. 11. Chromatogram of di-*n*-alkyl phthalates in isopropanol as mobile phase. Stationary phase: alkathene (10 wt-%) on Sil-O-Cel (firebrick), 50/70 mesh. $T = 245\,°C$, $P = 49.5$ bar. Column: 2 m × 6 mm ID (after [14]).

the members of the series with an odd number of C-atoms in the alcohol component (di-*n*-C_9, di-*n*-C_{11}...) had also been present, the resolution would naturally have been less satisfactory. However, a pressure program may be assumed to have improved the resolution and the peak width of the higher members of the series.

5. Basic Considerations

The usefulness of supercritical fluid chromatography, like that of other chromatographic techniques, depends on the resolution R. Hence, probably the most important single equation in chromatography is

$$R = \frac{1}{4} \cdot \frac{\alpha - 1}{\alpha} \cdot \frac{k'_2}{1 + k'_2} \cdot \sqrt{N} \qquad (3)$$

which links R with other fundamental chromatographic parameters

$$\alpha = \frac{k'_2}{k'_1} = \frac{K_2}{K_1}; \quad k'_2 > k'_1 \qquad (4)$$

where the subscripts 1 and 2 refer to two different compounds whose resolution is in question, and k' and K are the capacity ratios and partition coefficients, respectively [Eq. (2)]. The number of theoretical plates N is given by $N = L/H$, where L = column length and H = height of a theoretical plate. The second term $(\alpha - 1)/\alpha$ requires that $\alpha > 1$. This must be achieved by proper choice of mobile fluid and stationary phase, otherwise no resolution is obtainable even with a high number of theoretical plates. The third term $k'_2/(1 + k'_2)$ changes very

little at $k'_2 > 20$. However, in fluid chromatography k' might become rather small if the pressure is raised too high.

Homologous series are suitable test cases to determine whether $\alpha > 1$ can be achieved, since neighboring members become progressively closer in physical properties on proceeding to higher members of the series. In Figure 12 the k' values of propane, *n*-butane, and *p*-pentane, as measured on a silica/squalane column with CO_2 as the mobile phase, are given as a function of pressure[6].

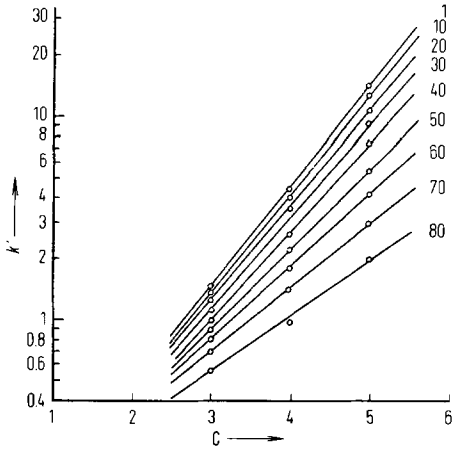


Fig. 12. Capacity ratios k' of *n*-alkanes with 3, 4 and 5 carbon atoms in CO_2 as mobile phase, plotted with the pressure P_{CO_2} (in kp/cm²) as parameter. Stationary phase: squalane on Sil-O-Cel, 50/70 mesh. $T = 40$ °C. Column: 1 m × 6 mm ID (after [6]).

The graph shows that the differences in k' between neighboring species are considerable in an isobaric operation and that they are still sufficient to enable separation of these compounds on using an upward pressure program of reasonable rate. Analogous conclusions can be drawn for isobaric runs from the measured capacity ratios of the *n*-paraffins up to C_{13} (Fig. 13)[40].

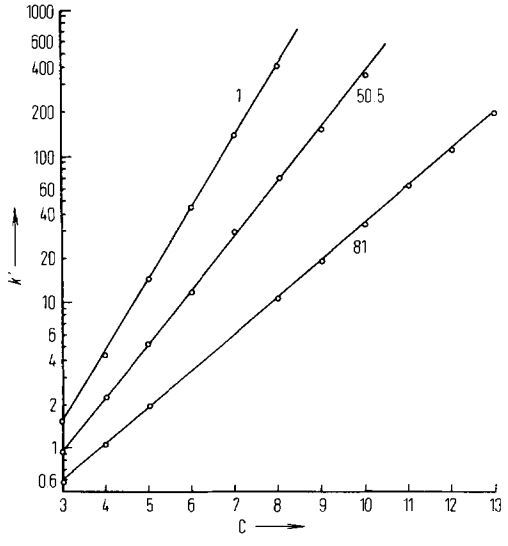


Fig. 13. Capacity ratios k' of *n*-alkanes with 3 to 13 carbon atoms in CO_2 as mobile phase at 40 °C, plotted with pressure P_{CO_2} (in kp/cm²) as parameter. Stationary phase: 23 wt-% squalane on Sil-O-Cel. 50/70 mesh. (after [40]).

If $R = 1$ suffices one obtains from Eq. 3 and values for $(\alpha - 1)/\alpha$ between 0.50 and 0.70 and for $k'_2/(1 + k'_2)$ between 0.5 and 0.9 a value for N which is between 50 and 300 theoretical plates. This number of plates is not difficult to achieve with column lengths of 2 or 3 m (cf. Figs. 15 and 16).

Measuring the k' values for a series of di-*n*-alkyl phthalates using different combinations of stationary and mobile phases indicated favorable α-values when a nonpolar stationary phase (Alkathene, a low molecular weight polyethylene) was employed in conjunction with a polar mobile phase (isopropanol) at 245 °C between 30 and 49.5 bar[14]. In contrast, on using a polar stationary phase (polyethylene glycol 6000) in conjunction with a nonpolar mobile phase (*n*-pentane) at 213 °C and pressures between 35 and 44.9 bar, smaller α-values were obtained. On investigating the latter combination of phases, the temperature dependence of k' at 35 bar revealed, however, a strong variation of α with temperature (Fig. 14)[14].

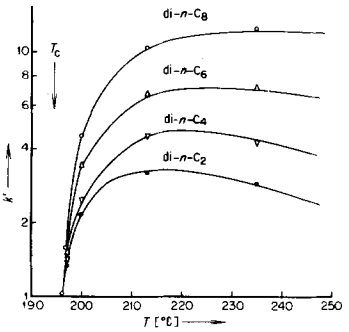


Fig. 14. Capacity ratios k' of di-*n*-alkyl phthalates with 12—24 carbon atoms plotted as function of temperature. Stationary phase: polyethylene glycol 6000 (≈23 wt-%) on Sil-O-Cel, mobile phase: *n*-pentane at 35 kp/cm² (after [14]).

A similar series of measurements at constant density instead of at constant pressure is called for in order to determine whether this is in part an effect of temperature and not primarily of a change of density with temperature.

The number of theoretical plates, N, is inversely proportional to the plate height H. Therefore the peak-broadening mechanisms which oppose resolution might be discussed in terms of H. In Figure 15 a plot of H *vs* the average interstitial linear velocity of the mobile phase, $\bar{v}$, is shown for CO_2 as the mobile phase and *N*-pentane as the substrate[38]. The plate heights are seen to increase strongly with $\bar{v}$ and with pressure. The increase with pressure, however, becomes smaller above 30 bar. Customarily, H is expressed in the form of the van Deemter equation:

$$H = A + \frac{B}{\bar{v}} + C\bar{v} \qquad (5)$$

By extrapolation of the high velocity part of the curves to $\bar{v} = 0$ it is likely that $A > 0$. On the other hand, A is not the major contributor to H at higher $\bar{v}$. The same holds true for $B/\bar{v}$, which in gas chromatography gives rise to a minimum in the curve, small remainders of which are seen in the 5 and 10 bar curves. Hence, it is the term $C\bar{v}$ which renders the largest contribution to H at already moderate $\bar{v}$.

Equation 5 may be written in full as[41,42]:

$$H = 2\lambda d_p + \frac{2\gamma D_m}{\bar{v}} + \left\{ 2\frac{k'_2}{(1+k'_2)^2} t_s + \frac{\omega \cdot d_p^2}{D_m} \right\} \bar{v} \qquad (6)$$

where λ = packing correction factor (≈ 0.5), d_p = particle diameter, γ = tortuosity factor (≈ 0.7), D_m = solute diffusion coefficient in the mobile phase, t_s = mean residence time of the solute molecule in the stationary phase, after leaving and re-entering the mobile phase, and ω = a flow path dependent term.

The first term (A) in Eq. (6) accounts for the longitudinal convective mixing as a cause of peak-broadening. This mixing is due to the interstitial flow pattern and is velocity independent. The second term $B/\bar{v}$ describes the longitudinal diffusion as a cause of peak broadening. Since the relative magnitude of D_m is small and $\bar{v}$ is usually relatively large, the second term can probably be neglected in many cases, a view which is supported by Figure 15. The third term ($C\bar{v}$) consists of

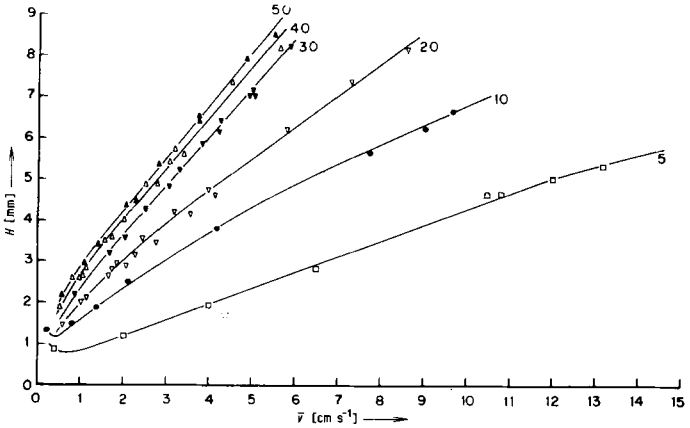


Fig. 15. Plate height H as a function of the velocity $\bar{v}$ of the fluid phase CO_2 at 40 °C, plotted with P_{CO_2} (in kp/cm^2) as parameter. Stationary phase: squalane on Sil-O-Cel, 50/70 mesh. Substrate: n-pentane (after [38]).

two additive components. The first accounts for nonequilibrium in radial transport of the substrate between mobile and stationary phase. It becomes small when k' is large as well as when t_s is small, *i.e.* when there is a high rate of solute transfer from and to the stationary phase. For these conditions, a pressure as small as possible and a temperature as high as possible, together with as thin a layer of stationary liquid as possible on the carrier particle may be of advantage. The second component of C may be looked upon as due to the hindered diffusive and convective radial transport of the substrate in the

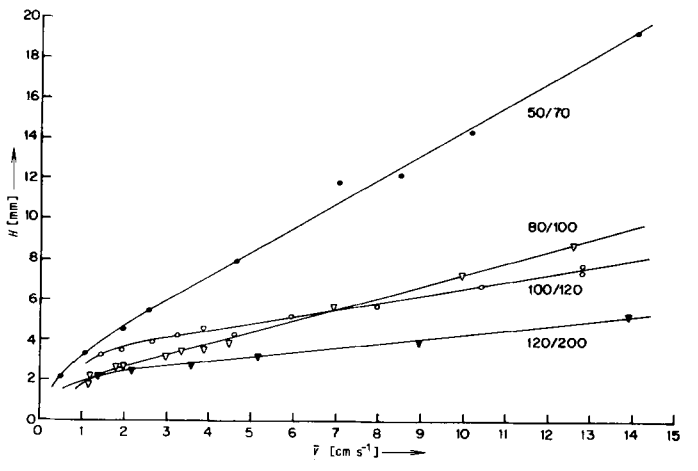


Fig. 16. Plate height H as a function of the velocity $\bar{v}$ of the fluid phase CO_2 at 40 °C and 57 kp/cm^2, plotted with the particle diameter d_p (in mesh) as parameter. Stationary phase: squalane on Sil-O-Cel. Substrate: n-pentane (after [38]).

mobile phase between the different velocity regimes within the interstitial flow pattern. Here a small particle size, higher temperature, and probably turbulent flow is of advantage. The high diffusion coefficients and the low viscosities previously discussed are important for both components of C, because they will lead to a decrease in t_s and ω.

It has been shown[38] by changing the particle diameter d_p that the second component of C is in fact the most important at higher pressures and velocities, at least for porous particles. In Figure 16 it is shown that a reduction in d_p, with other conditions being kept equal, leads to a large decrease in H. With the smallest particle diameter, other contributions to H are negligible, apart from the contribution of the A-term[38].

6. Outlook

A glance at the literature reveals an ever-increasing interest in the technique of chromatographic separation with supercritical fluid phases and in the development and design of more sophisticated, yet reliable and easily manipulated equipment, as are available commercially for gas- and liquid chromatography. Essential requirements are apparatus which enable automatic pressure control and programming as well as the usual temperature programming presently employed in gas-chromatography.

Research effort is also being directed to investigations on the influence of the type of mobile phase on dissolution and other relevant chromatographic parameters, *e.g.* in the series propane to hexane. It is to be expected that the mobile phase plays a more significant role in chromatography with supercritical fluid phases than in, say, gas-chromatographic separations. In this connection the possibilities arising from high Reynolds numbers and thus turbulent flow ought to be checked regarding their practical utility for increasing the efficiency of separation. Moreover, no investigations have, as yet, been performed with composition gradients of binary mobile phases.

Conventional stationary phases as used in gas and liquid chromatography, and newly developed ones including bound phases and porous layer beads should be examined more thoroughly with regard to their performance in fluid chromatography. Apart from conclusions based on analogies, it is not yet apparent which stationary phases are best suited for chromatography with supercritical fluid phases. Particle size and interparticle volume should, however, be considerably smaller than for gas chromatography.

The effects of pressure gradients along the separating column represent a methodological characteristic of fluid chromatography. No such pronounced effect of pressure gradient on the solvent power and other properties of the mobile phase is observed in gas- or liquid chromatography. This feature of chromatography with supercritical fluid phases should be explored for improving separations.

A recent development will also be utilized, *viz.* selective extraction with fluid phases, followed by normal thin-layer chromatography for identification and further resolution[43].

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The Separation of Nonvolatile Substances by Means of Compressed Gases in Countercurrent Processes[**]

By Siegfried Peter and Gerd Brunner[*]

Mixtures of nonvolatile and heat-sensitive substances can be separated by means of compressed gases in countercurrent processes. Moreover, such separations can be carried out at lower temperatures than in vacuum distillation. Addition of an entrainer enables alteration of the relative volatilities of the components. That such a method of separation is feasible on a large scale is illustrated using as example the separation of monoglycerides from a mixture of oleic glycerides at *e.g.* 110°C/135 bar. Propane is used as compressed gas, and acetone as entrainer.

1. Introduction

It has been known since the work of *Hannay* and *Hogarth*[1] in 1879 that compressed gases dissolve substances of low volatility. In industry it was the unfavorable aspects of this phenomenon that first manifested themselves. During the development of high-pressure hydrogenation it was observed, for example, that lubricating oil dissolved in the compressed gas led to diminished lubricating efficiency. Furthermore, the dissolved oil caused problems in subsequent processes. The use of increased operating pressures in power stations led to dissolution of salts in high-pressure steam. These salts precipitate on the turbine blades as the high-pressure steam expands. During the production and processing of oil it proved necessary to carry out detailed investigations on retrograde and anomalous vaporization, both experimentally as well as theoretically.

It is understandable, therefore, that the first proposals to utilize the phenomenon of solubilization in compressed gases as the basis of a separating process came from the petroleum industry. *Messmore*[2] in 1943 was perhaps the first to propose the use of supercritical hydrocarbons at high pressures for the deasphalting of oil. In 1955 *Zhuze* and *Kapelyushnikov*[3] described a process for removing resin from crude oils by means of supercritical propane at high pressures. In 1958 *Zhuze, Jushkevic* and *Gekker*[4] patented a process for the extraction of lanolin from wool grease. In the past two decades several separation processes involving the use of compressed gases have been proposed, *e.g.* the removal of caffeine from

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raw coffee by *Zosel*[5] in 1964, the production of spice extracts by *Vitzthum* and *Hubert*[6] in 1972, and the extraction of coal by *Whitehead* and *Williams*[7] in 1975.

The efficiency of a separation with compressed gases as solvent can be increased considerably in multistage countercurrent processes. *Zosel*[8] suggested such a procedure using conditions under which solubilization in the compressed gas decreases with increasing temperature, while *Ellis*[9] has discussed a process involving refluxing part of the nonvolatile material separated from the gas stream.

The efficiency of a multistage process can be increased still further by using an entrainer. The solubility can be increased and the nonvolatile substances can be removed from the compressed gas without expansion and recompression[10].

It will be shown, using as example the separation of the monoglycerides from a mixture of oleic acid glycerides, that a countercurrent process using compressed gases is technically feasible. In addition the economic aspects of the process will be discussed.

2. Physical Principles

For selection of suitable operating conditions, the phase equilibria of the relevant systems have to be known as a function of pressure, temperature and concentration of the different components. Under suitable conditions the concentration of the nonvolatile components can be increased by a factor of more than 10^{10} over that expected from vapor pressure data. Results obtained during investigation of the solubility of oleic acid in supercritical ethylene, are shown in Figure 1. The relative increase in concentration (= apparent increase in vapor pressure) of oleic acid is plotted against density on a logarithmic scale; some isobars and isotherms are shown. The relative increase in concentration of oleic acid increases with increasing density of the compressed gas up to a value of 10^9, approaching the critical point. The effect is primarily due to interaction forces between the molecules of oleic acid and those of the ethylene.

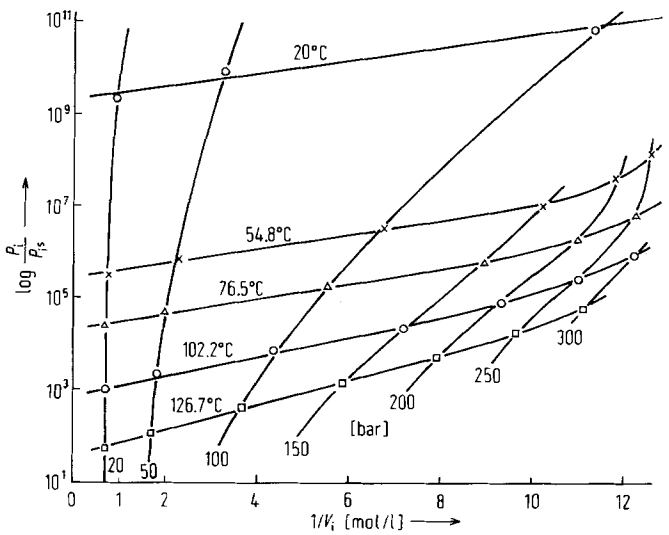


Fig. 1. Relative increase in concentration (P_i/P_{i^0}) of oleic acid in the gas phase as a function of density of the compressed gas in the system oleic acid/ethylene.

The effect of temperature on the solubility of a substance in a compressed gas changes with pressure. This can be seen from Figure 2, which shows the solubility of naphthalene in compressed ethylene as a function of temperature at different pressures as recorded by *Tsekhanskaya*, *Yomtev* and *Mashkina*[11]. Slightly above the critical temperature of the compressed gas, a rise of temperature at moderate pressures results in a decrease of solubility of the difficultly volatile component. At high pressures, a rise in temperature causes an increase in the solubility. This behavior can be understood, if the density of the compressed gas is considered as decisive for the solubility of the nonvolatile component in the gaseous phase.

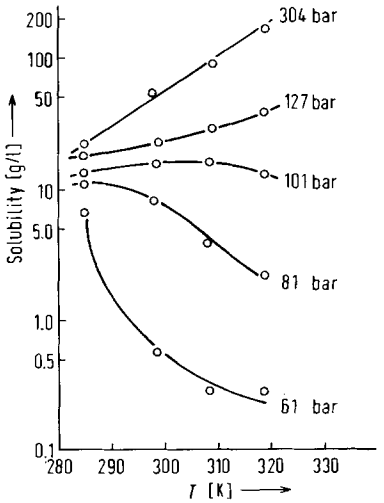


Fig. 2. Solubility of naphthalene in compressed ethylene *vs.* temperature at various pressures.

A rise in temperature at constant pressure leads, on the one hand, to a decrease in density of the compressed gas, and, on the other, to an exponential increase in the vapor pressure of the nonvolatile components. Figure 3 shows,

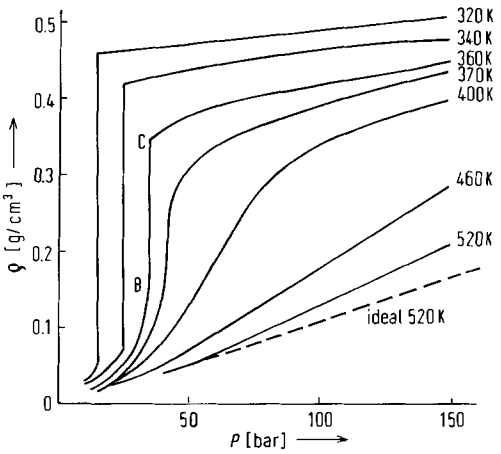


Fig. 3. Density of propane as a function of temperature and pressure. B = dew point, C = boiling point.

as example, the change in density of propane as a function of pressure and temperature. Slightly above the critical temperature, the density of the compressed gas at moderate pressures is lowered by a temperature rise to such an extent that the concentration of nonvolatile components in the gaseous phase decreases considerably. At high pressures the decrease of density caused by the temperature rise is so small that

the increase in vapor pressure leads to a higher concentration of the nonvolatile components in the gaseous phase.

In most cases, the relative volatilities of the components to be separated are only slightly influenced by the compressed gas. Hence, for mixtures of substances with small relative volatilities it is recommended that an entrainer be employed. The function of the entrainer is to increase the solubility of the nonvolatile components in the compressed gas as well as to facilitate their separation from the circulating gas at constant pressure. In such a way costs of recompression can be avoided. Furthermore, the entrainer can also increase the separation factor of the nonvolatile components.

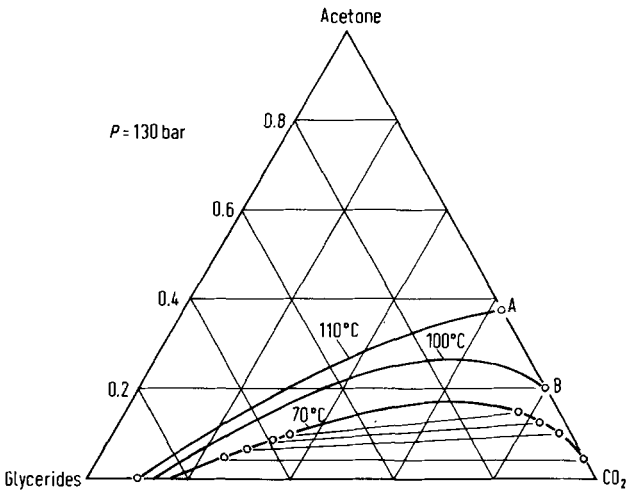


Fig. 4. Phase equilibria of the quasiternary system CO_2—acetone—glycerides of oleic acid at 130 bar and 70, 100 and 110°C. A, B see text.

Figure 4 shows the phase equilibria of the quasiternary system CO_2—acetone—oleic glycerides at a pressure of 130 bar and 70, 100 and 110°C. In the quasiternary system the content of glycerides in the gaseous phase is appreciably higher than that in the quasibinary system CO_2—oleic glycerides. In the temperature range over which the ternary system was examined, the glyceride content of the gaseous phase at constant pressure increases with decreasing temperature.

At 100°C and 70°C the binary system CO_2—acetone is supercritical at 130 bar. Under these conditions, only the system CO_2—oleic glycerides shows a miscibility gap. Figure 4 shows, moreover, that an appreciable enrichment of glycerides in the compressed gas is possible in the region near the critical point. At 130 bar and 110°C the binary system CO_2—acetone is subcritical. The miscibility gap is marked by points A and B on the diagram. At constant pressure and higher temperatures, the ability of the gaseous phase to take up components of low volatility is poor.

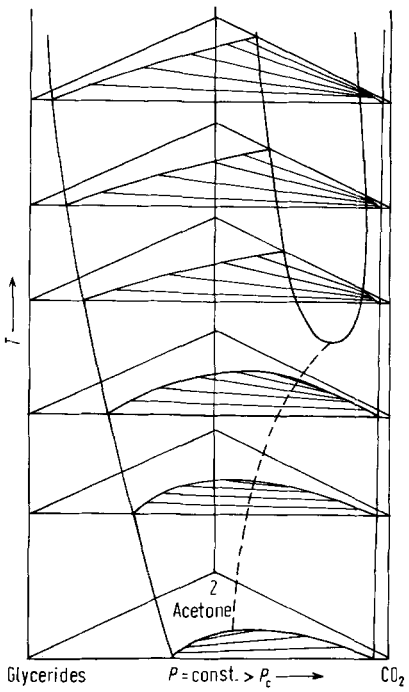


Fig. 5. Three-dimensional plot of the phase equilibria in the system CO_2—acetone—glycerides of oleic acid.

The phase equilibria of the system CO_2—acetone—oleic glycerides are shown in Figure 5 on a three-dimensional plot as a function of temperature and pressure.

Some experimental results of the phase equilibria in the quasiternary system CO_2—acetone—oleic glycerides are listed in Table 1. The concentration of glycerides in the gaseous phase is given as a function of the acetone content. In the last column the separation factor between mono- and diglyceride is shown. It can be seem that the separation factor decreases with increasing amount of entrainer—on approaching the critical point the separation tends towards unity.

Table 1. Phase equilibria in the system oleic triglycerides (1)—oleic diglycerides (2)—oleic monoglycerides (3)—glycerol (4)—acetone (5)—CO_2 (6). T = 69.6°C; P 132.5 bar. α_{32} = separation factor monoglyceride/diglyceride.

	Liquid phase			Gaseous phase			
Exp. No.	$x_1+x_2+x_3+x_4$	x_5 [wt. %]	x_6	$y_1+y_2+y_3+y_4$	y_5 [wt. %]	y_6	α_{32}
1	79.1	—	20.9	0.4	—	99.6	—
2	66.3	5.5	28.2	0.3	4.2	95.5	>100
3	57.5	7.7	34.8	2.7	10.0	87.3	30
4	51.1	9.6	39.3	4.3	12.4	83.3	3
5	45.8	11.1	43.1	8.9	14.8	76.3	1.4

3. Apparatus and Process

As described above, phase equilibria make it possible to separate nonvolatile substances at relatively low temperatures.

The process will be discussed with the aid of a schematic diagram of the apparatus used in the investigations (Figure 6). The apparatus consists of two columns, the first of which is used for the separation of the nonvolatile substances and the second is used for the separation of the nonvolatile components from the circulating gas.

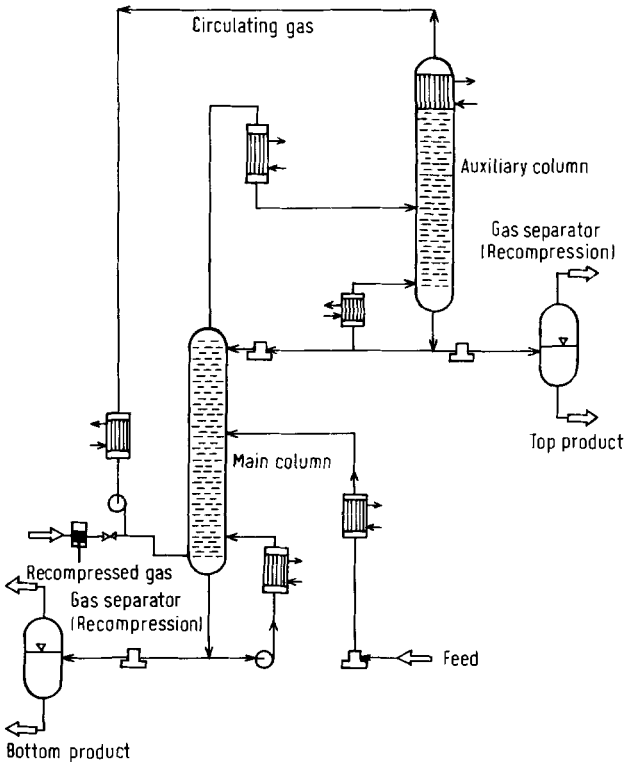


Fig. 6. Flow diagram of apparatus for the countercurrent separation of nonvolatile substances by means of compressed gases.

The mixture to be separated is fed together with the entrainer into the middle section of the main column. The stream of compressed gas leaving the top of the rectifying section of the main column is fed into the lower section of the auxiliary column. At the top of this column the gas stream flows through a heat exchanger, where part of the entrainer condenses. This refluxes countercurrently to the circulating gas and strips it of nonvolatile components. A heat exchanger at the bottom of the auxiliary column heats the mixture of nonvolatile substances and entrainer when required. The product withdrawn from the bottom of the auxiliary column is split into top product and reflux for the main column. The circulating gas, which consists of compressed gas with a certain proportion of entrainer, and which has, to a large extent, been freed of nonvolatile components, leaves the auxiliary column at the top and is returned to the bottom of the main column by means of a circulating pump. It is thus, possible to omit expansion and recompression of the circulating gas. At the bottom of the main column the nonvolatile substances dissolve in the gas phase. Here, the bottom product is also withdrawn.

It follows from Figure 4 that the binary system of compressed gas and entrainer in the main column must be under supercritical conditions in order to achieve a high concentration of nonvolatile substances in the gas phase. In the second column operating conditions have to be chosen under which the binary system, gas and entrainer, is subcritical. Under such conditions a fraction of the entrainer condenses and washes out the nonvolatile components from the circulating gas. The entrainer should have a boiling point lower than the decomposition temperature of the nonvolatile components, or it should be removable by extraction.

For the experimental investigations an apparatus made of strainless steel (1.4571) was employed. The bubble-cap columns have an internal diameter of 65 mm and are designed for an operating pressure of 150 bar at 120 °C. The main column contains 51 plates, the second column 34 plates.

4. Experimental Results

The separation of glycerides was investigated experimentally at a pressure of 135 bar and a bottom temperature of 80 °C in the main column. The temperature at the top of the auxiliary column was 110 °C. It should not fall below 100 °C, as the mixture acetone—CO_2 would then consist of only one phase. The content of nonvolatile substances in the circulating phase in the auxiliary column could be lowered to about 0.008 wt-%, 1/500 of the amount in the main column.

Using a reflux ratio of 1.5, under the above given conditions, the monoglyceride concentration in the top product of the main column amounted to 95 % of the total glycerides. A feed of 1.25 kg/h yielded a top product of 0.65 kg/h. With a reflux ratio of 2, the top product contained practically no diglycerides. This can be seen from the gas chromatograms of feed and top product shown in Figure 7.

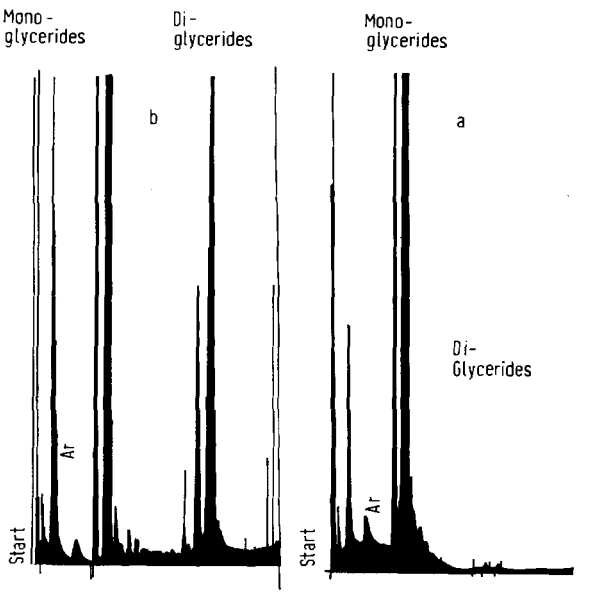


Fig. 7. Gas chromatograms of glycerides: a) top product and b) feed.

5. Economic Aspects

The results of the experiments described above on the separation of monoglyceride from a mixture of glycerides could be used as a basis for the estimation of investment and operating costs of a plant for the separation of substances by means of compressed gases in a countercurrent process. The costs were estimated according to a method described by *Kölbel* and *Schulze*[13]. The costs of the individual items of equipment

were determined using the September 1977 price index, published in the journal "Chemische Industrie"[14]. The results of the cost estimation for separating a mixture of glycerides containing 45 wt.-% monoglycerides are listed in Table 2.

Table 2. Cost estimation for the separation of glycerides. Method: see [13]. Price index: September 1977 [14]. Throughput 250 g m^{-2} sec^{-1} nonvolatile components. Operating conditions: 135 bar; 110°C; oleic glycerides with *ca.* 10 wt-% acetone as entrainer and propane as compressed gas.

Product	[t/a]	5000	15000	30000
Column diameter	[m]	1.56	2.70	3.83
Total cost of plant	[DM]	8500000	13100000	20800000
Depreciation 10 %	[DM]	850000	1310000	2080000
Capital risk 1 %	[DM]	85000	131000	208000
Calculated interest	[DM]	374000	576400	915200
Energy costs	[DM]	25000	30000	50000
Payroll	[DM]	250000	250000	250000
Overheads	[DM]	125000	125000	125000
Maintenance	[DM]	425000	655000	1040000
Total costs	[DM]	2134000	3077000	4668000
Processing costs	[DM/kg]	0.43	0.20	0.15

If the process is carried out at lower pressures, the reduction in costs is considerable (Table 3). An investigation revealed that this reduction in the operating pressure is possible with suitably chosen supercritical component and entrainer.

Table 3. Comparative costs at different operating pressures. Processing costs in DM/kg top product.

Size of plant (Amount of product)	5000 t/a	15000 t/a	30000 t/a
Operating pressure [bar]	Processing costs [DM/kg]	[DM/kg]	[DM/kg]
135	0.43	0.20	0.15
95	0.35	0.16	0.12
80	0.31	0.15	0.11

In Tables 2 and 3 only the costs for the high-pressure distillation have been considered. The costs for separation of the product streams from the entrainer have not been taken into consideration.

6. Discussion of Results

The choice of entrainer will depend not only on thermodynamic considerations but also, *inter alia*, on its physiological effects and price.

For the selected operating conditions the densities of the two phases differ by a factor of 3—8, a difference which is considerably higher than in an extraction process. The ratio of the phase densities for a given pressure and temperature depends mainly on the entrainer concentration.

The proportion of nonvolatile components in the gaseous phase increases with increasing concentration of entrainer, but the separation factor decreases. It is therefore necessary to choose a favorable mode of operation between two competing conditions: a large concentration of entrainer leads to a high concentration of nonvolatile components in the gaseous phase, but because of poor separation per stage, a large number of stages is necessary; a low concentration of entrainer leads to a low concentration of nonvolatile components; however, only a few stages are then required.

As in rectification, the separation in the present process improves with increasing reflux ratio. For a given product stream, a higher reflux ratio requires a larger column diameter. As this results in a considerable increase in price of the pressure vessels, it would be preferable to choose tall, slim columns with relatively low reflux ratios rather than short columns of large diameter.

In general, mixtures of nonvolatile and heat-sensitive substances can be handled in this process, at temperatures far lower than those encountered in vacuum distillation. The method described here appears particularly suitable for the processing of materials which are easily oxidized—at such elevated pressures there is no danger of oxygen entering the equipment.

Since the relative volatilities of components can be altered by addition of entrainer, the new process not only provides an alternative to vacuum and molecular distillation, but also enables the advantages of extractive distillation to be exploited for the separation of mixtures of slightly volatile compounds.

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Large-Scale Industrial Plant for Extraction with Supercritical Gases[**]

By R. Eggers[*]

Criteria for the design and construction of plant for obtaining carrier material or extracts are discussed for the example of the extraction of natural products with supercritical carbon dioxide. The parameters to be established and the course of the process in a large-scale plant are indicated. Plant engineering and optimization must be attuned to specific process-technological and construction problems.

1. Introduction

In order to exploit the phenomenon of good solubility of difficultly volatile substances in compressed supercritical gases, increasing attention has been devoted to the planning of processes and equipment and the design of suitable large-scale plant.

High-pressure extraction with carbon dioxide represents a potential method for the separation of thermally unstable materials such as natural products. The resulting advantages cannot be attained by classical separation processes. The design and construction of such plant for the extraction of natural products with supercritical CO_2 will be reviewed below with due emphasis on the important features.

2. Plant Design Criteria

The concept of a plant for high-pressure (HP) extraction of natural products must be based upon the desired aim of production with due consideration of the starting materials. Two fundamental possibilities should in principle be distinguished:

a) *Carrier material separation.* This is the situation where the starting material constitutes the final product after the removal of certain components by an extraction process. Examples are the production of decaffeinated coffee and of nicotine-free tobacco.

b) *Extract material separation.* Here the carrier material is regarded as a virtually valueless matrix from which the extract is obtained, for example hop extract, cocoa butter, and extracts of spices.

In order to provide a numerical basis for the plant dimensions and for detailed design of the structural components, it is necessary that a number of process data be known or determined:

a) Output capacity;

b) The mode of operation of the plant (continuous production or occasional shutdowns);

c) The bulk density of the material to be extracted;

d) The mass ratio of CO_2 and the material to be extracted;

e) The extraction time.

If the above-listed data are known or specified, it becomes possible to calculate the required extraction volumes and hence the size of the vessels and pipe cross-sections.

The operating pressures and temperatures are further fundamental parameters for the design of an extraction plant with the use of supercritical gases. Apart from process-technological data (such as the required input and output of energy) the above fundamental parameters also determine the plant design characteristics. One problem that should not be underestimated is the precise knowledge of the material properties of the solvent, the starting material, and the extract which, in many cases because of the absence of literature data, can only be obtained by laboratory determinations.

Pressure drops may be calculated on the basis of models, but if the starting material is unusual with regard to shape or consistency they must be determined in preliminary experiments.

3. Process Description

Products dissolved in a supercritical gas may be separated out by pressure reduction and/or by changing the temperature[1-4]. Separation by changes in temperature will not be discussed here, because this entails the loss of important constituents in the case of thermolabile natural products.

Plant for separating solute from solvent by pressure reduction is, in principle, characterized by the following main stages:

1) Extractor vessel in the extraction stage;
2) Pressure reduction at a throttle;
3) Demixing container in the separation stage;
4) Pressure increase in a pump or a compressor.

The principal course of events in a one-stage process is described in greater detail below. It may be readily followed by means of Figures 1 and 2 and by referring to a block diagram and the associated flow chart.

Preparation of the material to be extracted. The material may be comminuted (chopped or ground) or it may be treated by swelling with steam or water.

Charging of the plant. The quantity of solvent required for the extraction is determined precisely by the pressure and temperature conditions.

Heating to the extraction temperature. Heating is carried out isochorically by pumping the solvent through the steam-heated heat exchanger W1 using the pump P2 until the desired process conditions—supercritical pressure and supercritical temperature—have been attained in the extraction vessel A.

Extraction. The supercritical gas extracts the soluble components from the carrier material and is recycled *via* the throttle, the separator vessel B, the heat exchanger W2, the pumps P3 and P1, and the heat exchanger W1. The pressure reduction causes a precipitation of the extracted material in

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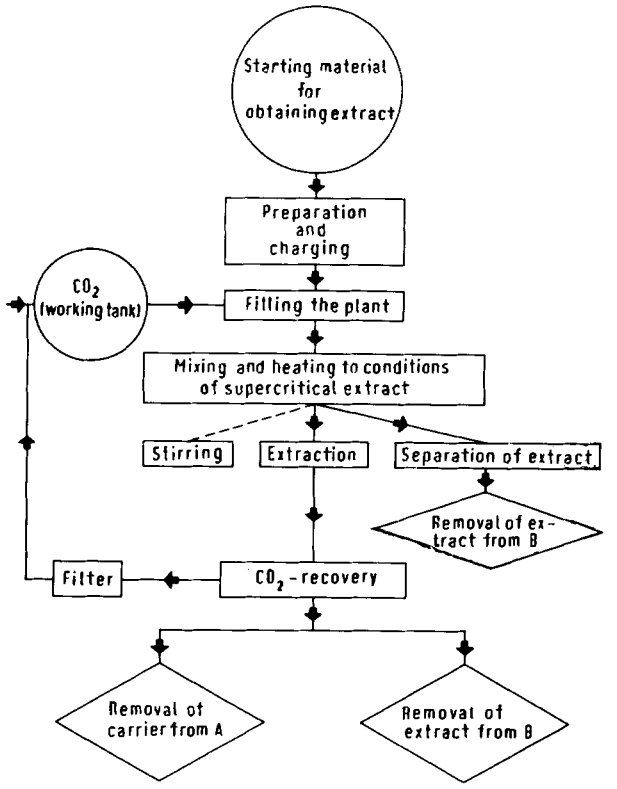


Fig. 1. Block diagram for extraction using supercritical CO_2 with the aim of extract isolation.

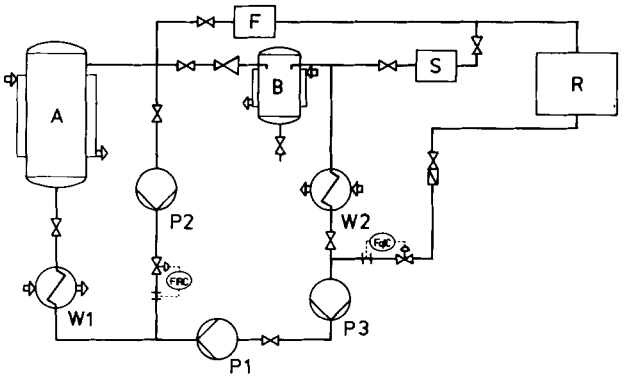


Fig. 2. Flow chart for obtaining the extract using supercritical CO_2. A, extraction vessel; B, demixing vessel; F, filter; S, sorption vessel; R, CO_2-recovery with working tank; P1, pressure build-up pump; P2, mixing pump; P3, preliminary pressure pump; W1, heater; W2, condenser; FRIC, mass flow governor; FqIC, quantity governor.

the separator vessel, from where it may be continuously removed by means of a bottom outlet. The medium must be completely liquefied in the condenser W2, so that suction can be applied from the liquid gas pump P1 and to make its circulation possible. The pressure rise to the extraction pressure in P1 is followed by raising the temperature to the extraction temperature in the heat exchanger W1. This completes the cycle.

Provision is made during extraction for periods of stirring the charge to prevent the formation of channels through which the supercritical gas could pass freely in the carrier material, since this would lead to local limitation of mass transfer.

Recovery. The solvent is returned to the working vessel from the extraction system *via* filter F, in order to prevent any contamination of the contents of this vessel with the extracted material. Finally the extraction residue is removed from the vessel A and the extract from the vessel B.

4. Thermodynamic Aspects

In order to obtain the thermodynamic data for a given step of the process it is particularly useful to have a phase diagram for the solvent used in the extraction. Many diagrams are available for CO_2, but they do not agree in all respects[5–8]. Temperature-entropy (T,s) diagrams are particularly suitable, because in these diagrams the heat energy supplied and removed in reversible processes is represented by areas.

In order to illustrate the course of events in a T,s diagram (Fig. 3), let us consider the extraction/demixing cycle, using representative values for the phase data.

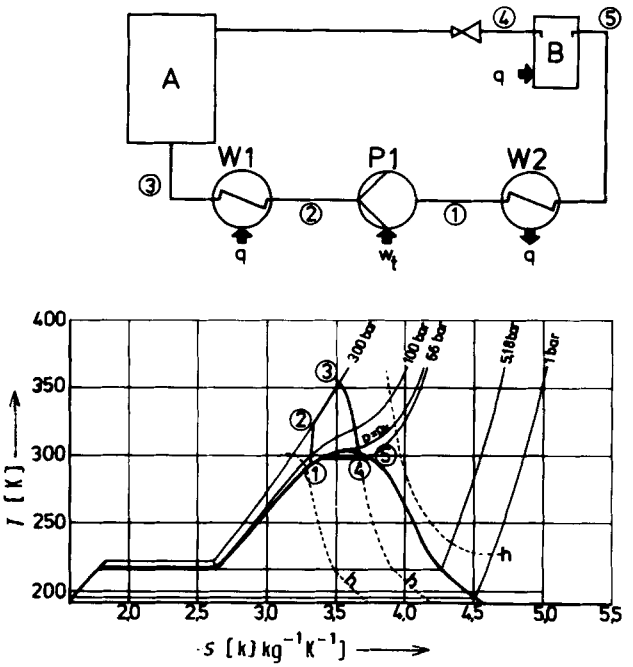


Fig. 3. Flow chart and phase diagram for a single-step cyclic extraction and demixing process. ①—②, compression in P1; ②—③, heating up in W1 under constant pressure; ③—④, adiabatic pressure release; ④—⑤, evaporation of the liquid fraction; ⑤—①, condensation and supercooling in W2 under constant pressure; q, heat flow; w_t, power supply; h, enthalpy.

The path from point 3 to point 4 corresponds to the adiabatic pressure release in the demixing vessel, the extract then separating out and undergoing precipitation. At point 4 the CO_2 is present as a wet vapor. The liquid fraction is evaporated by supplying heat, so that only the vapor without the extract is removed from B (point 5). This vapor is condensed in heat exchanger W2 and the liquid phase is supercooled (point 1). The solvent must then be compressed to the extraction pressure in pump P1 (point 1 to point 2). The solvent is finally heated at a constant pressure to the extraction temperature by supplying heat to W1 (point 2 to point 3).

It must also be established to what extent the process data would be modified if data for the charged phases actually present were to be used rather than those for pure CO_2. The thermodynamic consideration has the advantage that the solvation energies of the components that pass into solution are negligibly small compared with the enthalpy of the flowing medium.

5. Plant Technology and Optimization

Although the basic plant concept varies according to the starting material, it is possible to specify certain components and combinations of equipment common to all designs and for which the following characteristics are important:

- vessel design for high pressures (100 to 300 bar), with an allowance for an increasing stress
- compliance with the requirements of foodstuffs legislation, *i.e.* corrosion-resistant internal surfaces and surfaces that are easy to clean or decontaminate
- temperatures generally not exceeding 100 °C
- the bulk density of the starting material is sometimes extremely low.

The vessel-filling devices must be adapted to the widely varying properties of the natural materials under consideration. Granular material is relatively simple to handle, but loose bulk material, which can be compacted only with difficulty, presents certain problems. It will be necessary to examine possible designs for continuous operation in the latter case. Pretreatment such as grinding may be recommended if the material suffers no detrimental effects. Materials requiring special care are suitably placed in baskets that can be prepared in individual batches; this is generally appropriate for all natural products in which the leaf or the fiber structure must be preserved unchanged.

The design of closures is determined by the method of charging and discharging. Granular materials may be fed in or removed through the top or bottom of the vessel using a small funnel; in the case of baskets it must be possible to fully open the vessels. In such cases it is particularly necessary to provide for fast closure; there are comparatively few examples of the latter with the required dimensions in high-pressure vessel technology. One such design is shown in Figure 4.

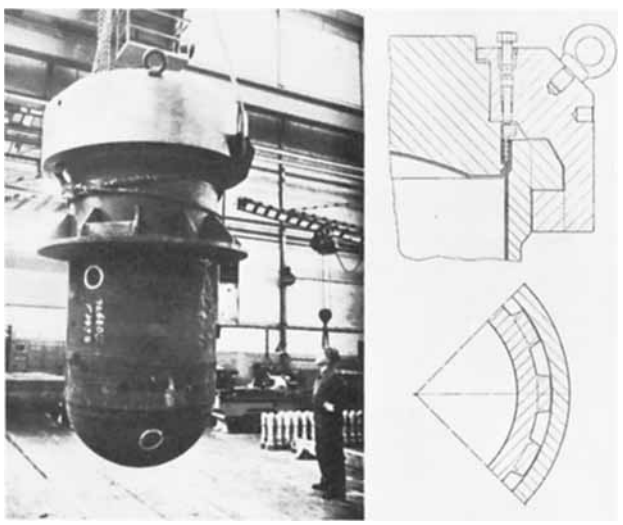


Fig. 4. A quick method of closure for a high-pressure vessel.

Pipe sections in which there is a risk of extract separation along the internal surface require the provision of external heating, for example by means of electric heating mantles.

The degree of automation of the plant is important. The following settings must be suitably selected and controlled in a plant in which the extraction is carried out with supercritical gases: quantities, mass flows, temperatures, pressure, and charge levels.

For the construction of a production plant the optimum working conditions must be known; these are determined on a pilot plant. Such a pilot plant must permit maximum possible variation of the operating conditions, in order to provide adequate data on the yield and quality of extract, and on the extraction times.

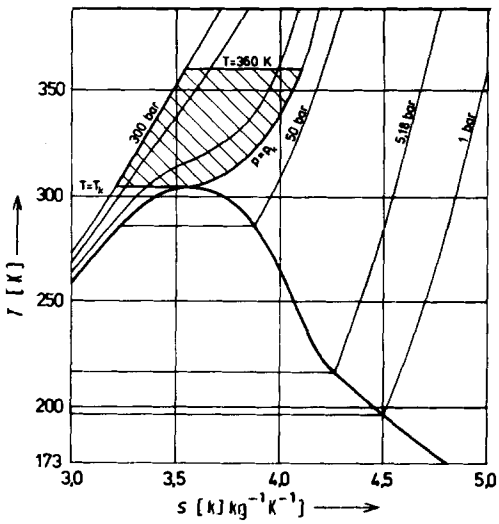


Fig. 5. Phase range for the extraction of natural products with supercritical CO_2.

The T,s diagram for CO_2 (see the shaded area within the supercritical region of Figure 5) clearly demonstrates the need for an extensive operating range of a pilot plant for the extraction of natural products in order to permit optimization of the operating conditions in the final production plant. Having thus determined the operating conditions and times for the individual process steps, it becomes possible to plot the course of the pressure and temperature *versus* time; an example of

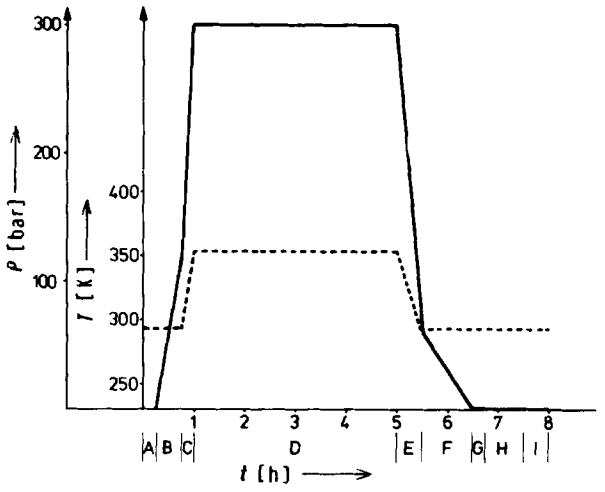


Fig. 6. Pressure (—) and temperature (----) in the extraction vessel as a function of time. A, charging of the extraction vessel; B, filling the plant with solvent; C, heating up to extraction conditions; D, removal of the extract and separation; E, venting down to tank pressure; F, evacuation to residual pressure; G, venting of the residual gas; H, removal of carrier material and extract; I, regeneration of the adsorbant.

this is given in Figure 6 for the single-step extraction process that has already been discussed.

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COMMUNICATIONS

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Thermal Degradation of Cellulose and Chitin in Supercritical Acetone

By *Peter Köll* and *Jürgen Metzger*[*]

In the thermal degradation of polysaccharides rapid removal of the primary products from the reaction zone is a decisive prerequisite for the use of this reaction on a preparative or industrial scale as regards obtaining a high-yield uniform product pattern. Customary pyrolysis methods lead, particularly on a large-scale, to secondary reactions accompanied by strong carbonization. This cannot be entirely avoided, even if the reaction is carried out *in vacuo*; moreover, the pyrolysis is then rendered difficult by the poor transfer of heat.

To overcome this problem, we have for the first time exploited the good dissolution properties of compressed gases in the supercritical state[1] in a flow apparatus. With this method we have been able to detect—to our knowledge for the first time—the primary product of the thermal degradation of chitin[2], namely 2-acetamido-1,6-anhydro-2-deoxy-β-D-glucopyranose[3], an important amino sugar used as starting substance for the synthesis of physiologically active oligosaccharides[4], and to isolate it on a preparative scale. Furthermore, cellulose could be degraded to the extent of 98%.

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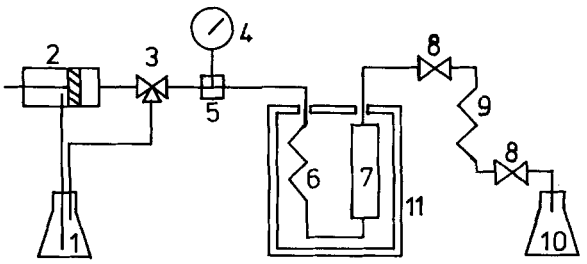


Fig. 1. Schematic diagram of the apparatus. 1) Solvent reservoir; 2) high-pressure pump for up to 500 bar (HPLC pump); 3) excess-pressure valve; 4) manometer for up to 600 bar; 5) T-piece; 6) pre-heater capillary (diameter 1.6 mm); 7) reactor (V = 50 ml), 8) valve; 9) heat exchanger (1.6 mm-diameter capillary); 10) collector; 11) GC furnace.

The apparatus used (Fig. 1) was largely made up of HPLC equipment; a GC furnace was used for heating. Acetone (T_c = 508.5 K, P_c = 47 bar) proved to be especially suitable as aprotic solvent. In a typical experiment, 18 g of microcrystalline cellulose (Merck; dry weight 17.1 g) was transferred to a preparative HPLC column and treated at a pressure of 250 bar with acetone at an average flowrate of 4.5 ml/min. The temperature was slowly increased from 250°C at the beginning of the experiment to 340°C at completion of the degradation (after 10 h). There remained an extraction residue of only 0.36 g (2.1 %). Concentration of the acetone solution *in vacuo* gave 18.3 g of a dark syrup, which was shown by thin-layer chromatography to consist mainly of low molecular products. The mass balance exceeded 100 %, since small amounts of difficultly volatile condensation products of acetone are also formed during the reaction. However, since evolution of gases during the reaction is very slight, it can be assumed that approximately 98 % of the cellulose is in fact liquefied. The main products could be identified, in particular, as anhydrosugars by comparison with authentic materials. The following amounts (based on consumed cellulose) were determined by quantitative gas chromatography of the acetates (Carlo Erba Fractovap 2300, column 2 m XE60, T = 473 K, injection block 523 K, 20 ml He/min, triacetyl-1,6-anhydrogalactofuranose as internal standard):
38.8 % 1,6-anhydro-β-D-glucopyranose ("glucosan"), 4.3 % 1,6-anhydro-β-D-glucofuranose, 4.0 % 1,4:3,6-dianhydro-α-D-glucopyranose, *ca.* 1 % 1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose.

The yield of glucosan can be regarded as excellent when compared with the yields obtained on vacuum pyrolysis[5]. The cellulose is extraordinarily gently degraded by acetone,

despite the high temperature. Thus, according to diffractometer measurements the residue still has the crystallinity of the starting cellulose even after 50 % degradation. Nor do scanning electron photomicrographs show any serious changes in the structure at this stage of the degradation.

Chitin (Fluka, techn., ash content 5 %; 15.0 g) was degraded in the same way as cellulose in the temperature range 250—340 °C at 250 bar by acetone at a flow rate of 5.0 ml/min over 7.5 h. The residue amounted to 2.3 g (15.3 %). Concentration of the acetone solution by evaporation afforded 16.4 g of a mobile black oil, which was shown by combined GC/MS to contain acetamide and diacetamide. Additional thin-layer chromatography showed the presence of 1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-eno-pyranos-2-ulose. Partition of the syrup between water and chloroform afforded 4.1 g of water-soluble product and 12.3 g of chloroform extract. The main sugar component 2-acetamido-1,6-anhydro-2-deoxy-β-D-glucopyranose[3] could be recovered from the water-soluble product in 5.6 % overall yield (0.8 g) by chromatographic separation on a silica gel column using acetone as eluent. The actual amount of this sugar in the pyrolysate is higher; but, further recovery by crystallization is rendered difficult by the degree of contamination with acetamide. However, in view of the ready accessibility of the starting material and the relative ease with which the reaction and isolation can be carried out, the yield is nevertheless preparatively acceptable.

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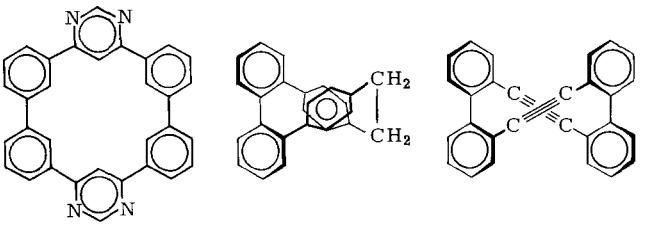
CAS Registry numbers:
Cellulose, 9004-34-6; chitin, 1398-61-4; 1,6-anhydro-β-D-glucopyranose, 9012-72-0; 1,6-anhydro-β-D-glucofuranose, 7425-74-3; 1,4:3,6-dianhydro-α-D-glucopyranose, 4451-30-3; 1,6-anhydro-3,4-dideoxy-β-D-glycerohex-3-enopyranos-2-ulose, 37112-31-5; 2-acetamido-1,6-anhydro-2-deoxy-β-D-glucopyranose, 37042-52-7

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[2] *R. A. A. Muzzarelli:* Chitin. Pergamon Press, Oxford 1977.
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[4] *Y. Rabinsohn, A. J. Acher, D. Shapiro,* J. Org. Chem. *38,* 202 (1973); *F. Schmitt, P. Sinay,* Carbohydr. Res. *29,* 99 (1973).
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Heterocyclohexaaromatic Compound with Face-to-Face Arrangement of Two Benzene Rings[**]

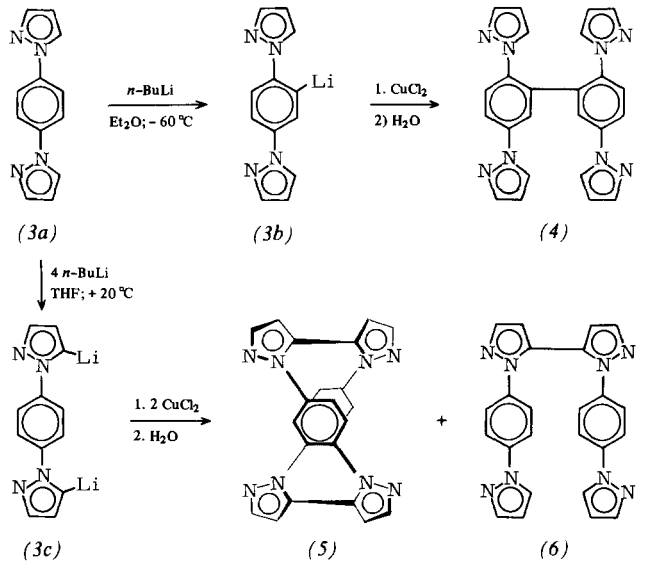
By *Thomas Kauffmann* and *Herbert Lexy*[*]

We previously reported the synthesis of the first heterocyclohexaaromatic compounds 4,6,4‴,6‴-tetraazahexa-*m*-phenylene *(1)*[1a] and 4,6,4′,6′,4‴,6‴,4⁗,6⁗-octaazahexa-*m*-phenylene[1b]. The ring members in these macrocycles are arranged in the form of a wreath, without their individual planes being twisted[1c]. Since compounds *(2a)*[2] and *(2b)*[3] are known, it was expected that cyclohexaaromatic compounds in which two rings lie one on top of the other, *i.e.* face-to-face[4], could also be synthesized. We have now been able to prepare the first compound of this type by the reaction sequence *(3a)* → *(3c)* → *(5)*.



(1) *(2a)* *(2b)*

The starting compound 1,4-phenylenedi(1-pyrazole) *(3a)*, previously only accessible in low yields by a ring-forming synthesis[5], could be obtained in 79 % yield from *p*-dibromobenzene and pyrazole by ring linkage. On treatment with 1 mol *n*-butyllithium in ether at −60 °C, *(3a)* was preferentially lithiated (kinetic control) at the benzene ring to give *(3b)*, which on reaction with $CuCl_2$ was converted mainly into *(4)* (28 %; m.p. 208—212 °C). In contrast, treatment of *(3a)* with 4 mol *n*-butyllithium in THF at +20 °C afforded almost quantitative yields of *(3c)*[6], whose coupling with $CuCl_2$ in the temperature range −70 to +20 °C gave the desired product *(5)* in the astonishingly good yield of 43 %. *(6)* was formed as by-product (5 %; m.p. 238—243 °C). The structures have been confirmed by elemental analysis, MS and ^{1}H-NMR data, and the melting points given are corrected.



(3a) *(3b)* *(4)* *(3c)* *(5)* *(6)*

According to the Stuart-Briegleb model the benzene rings of *(5)* are oriented face-to-face. The resulting interaction between their orbitals is revealed in the ^{1}H-NMR spectra ($CDCl_3$) by an upfield shift of the proton signals (s, $\delta = 6.97$) compared to *(3a)* ($\delta = 7.80$). This corresponds to the behavior observed in [2.2]paracyclophane[7], in *(2a)*[2], and in other strained phanes, and can be explained in terms of an anisotropic effect of the neighboring benzene ring[8]. Since the phenylene protons of *(5)* appear in the ^{1}H-NMR spectrum as a sharp singlet, despite different chemical environments, it may be assumed that *(5)* and its mirror image undergo fast interconversion. No splitting of the singlet could be observed at −80 °C [in ethanol/$CDCl_3$ (1 : 3)][9]; the temperature could not be lowered any further because of the sparing solubility of *(5)*.

Experimental

Synthesis of *(3a)*: A mixture of 1,4-dibromobenzene (2.36 g, 10.0 mmol), pyrazole (6.80 g, 100.0 mmol), K_2CO_3 (16.0 g,

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120.0 mmol), and CuI (5.00 g) in nitrobenzene (20 ml) is heated under reflux for 3 h. The volatile components are distilled off at 0.2 torr (bath temp. 100 °C) and the residue chromatographed on a silica gel column with dichloromethane. The third fraction eluted contains 1.64 g (79 %) of pure *(3a)*, m.p. 182 °C (Ref. [5]: 180 °C).

Synthesis of *(5)*: A stirred solution of *n*-BuLi (4.0 mmol) in ether (5 ml) is treated dropwise within 15 min at 25 °C with a solution of *(3a)* (210 mg, 1.0 mmol) in 20 ml THF. Stirring is continued for a further 30 min, whereupon a yellow precipitate separates out. The mixture is cooled to −70 °C, treated with 670 mg (5.0 mmol) of extremely dry $CuCl_2$, and then allowed to warm to room temperature within 12 h. After protolysis with 5 ml methanol, complexation of the copper salt with 100 ml conc. ammonia, and extraction several times with hot chloroform, the dried extract is concentrated by evaporation and the residue chromatographed on a silica gel column with dichloromethane/methanol (100:1). Recrystallization of the third fraction from chloroform affords 90 mg (43 %) *(5)* as colorless crystals which sublime at 300 °C/0.02 torr and decompose between 420 and 450 °C.

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CAS Registry numbers:
(3a), 67673-42-1; *(3b)*, 67673-43-2; *(3c)*, 67673-44-3; *(4)*, 67673-45-4; *(5)*, 67673-46-5; *(6)*, 67673-47-6; 1,4-dibromobenzene, 106-37-6; pyrazole, 288-13-1

[1] a) *Th. Kauffmann, B. Muke, R. Otter, D. Tigler*, Angew. Chem. *87*, 746 (1975); Angew. Chem. Int. Ed. Engl. *14*, 714 (1975); b) *B. Muke*, Dissertation, Universität Münster 1976; c) X-ray structure analysis of *(1)*: *H. G. von Schnering, G. Sawitzki* 1976/77, Max-Planck-Institut für Festkörperforschung in Stuttgart, private communication. The ^{1}H-NMR spectrum shows that the octaaza compound is also planar.
[2] *F. Vögtle, M. Atzmüller, W. Wehner, J. Grütze*, Angew. Chem. *89*, 338 (1977); Angew. Chem. Int. Ed. Engl. *16*, 325 (1977); cf. also *N. Jacobson, V. Boekelheide, ibid. 90*, 49 (1978) and *17*, 46 (1978).
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[4] *D. J. Cram, H. Steinberg*, J. Am. Chem. Soc. *73*, 5691 (1951).
[5] *B. M. Lynch, Y. Y. Hung*, Can. J. Chem. *42*, 1605 (1964), yield not quoted. Workup gave 5 % *(3a)*.
[6] For lithiation to *(3b)* or *(3c)*, see *Th. Kauffmann, A. Mitschker*, Tetrahedron Lett. *1973*, 4039.
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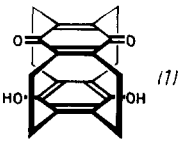
[2.2.2.2](1,2,4,5)Cyclophane Quinhydrone—A Donor-Acceptor Cyclophane with an Extremely Short Transannular Distance[1]

By *Heinz A. Staab* and *Volker Schwendemann*[*]

[2.2.2.2](1,2,4,5)Cyclophane[2] has extremely short distances of 2.69 Å between the four pairs of bridged carbon atoms of the aromatic rings[3]. The intramolecular quinhydrone *(1)* of this cyclophane was therefore of particular interest for our studies on the influence of distance and orientation on donor-acceptor interaction in cyclophane quinhydrones[1].

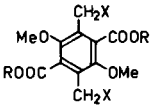
[*] Prof. Dr. H. A. Staab, Dipl.-Chem. V. Schwendemann
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1,4-Dibromo-2,5-dimethoxy-3,6-dimethylbenzene[4] was transformed *via* 2,5-dimethoxy-3,6-dimethylterephthalic acid

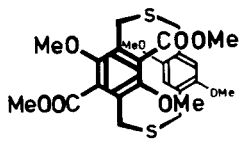


(1)

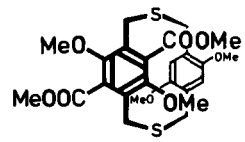
(2)[5] (*n*-butyllithium/ether; CO_2; 84 %; m.p. 250 °C) and the dimethyl ester *(3)*[5] (potassium salt, dimethyl sulfate/acetone; 90 %; m.p. 96 °C) into dimethyl 2,5-bis(bromomethyl)-3,6-dimethoxyterephthalate *(4)*[5] (*N*-bromosuccinimide/CCl_4; 79 %; m.p. 140 °C). Compound *(4)* could be cyclized with 1,4-bis(mercaptomethyl)-2,5-dimethoxybenzene[4] [simultaneous dropwise addition of the solutions of 5 mmol of each reactant in dioxane (200 ml) to potassium carbonate (4.5 g) in boiling methanol (400 ml) within 6 h]. The diastereomeric dithia[3.3]paracyclophanes *(5)* and *(6)* could be separated by chromatography on silica gel from ether/cyclohexane (1:1) and assigned on the basis of the ^{1}H-NMR spectra [*(5)*[5]: m.p. 195—196 °C, 23 % yield; *(6)*[5]: m.p. 173—174 °C, 8 % yield].



(2), X = H, R = H
(3), X = H, R = Me
(4), X = Br, R = Me

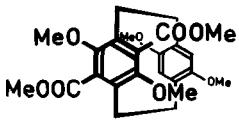


(5)

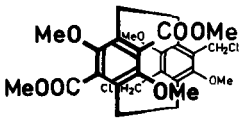


(6)

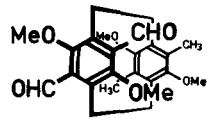
The mixture of *(5)* and *(6)*, like the pure stereoisomers *(5)* and *(6)*, on irradiation in trimethyl phosphite[6] (600-W Hg high-pressure lamp, 6 h), gave only one of the two possible 4,7,12,15-tetramethoxy-5,8-dimethoxycarbonyl[2.2]paracyclophanes, *viz.* *(7)*[5] (m.p. 168 °C, 68 % yield), which has the four methoxy groups in the desired pseudogeminal position and the more bulky methoxy carbonyl groups opposite the unsubstituted C atoms of the adjacent ring.



(7)



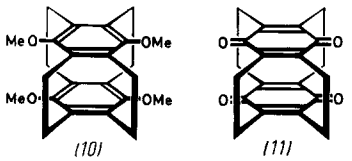
(8)



(9)

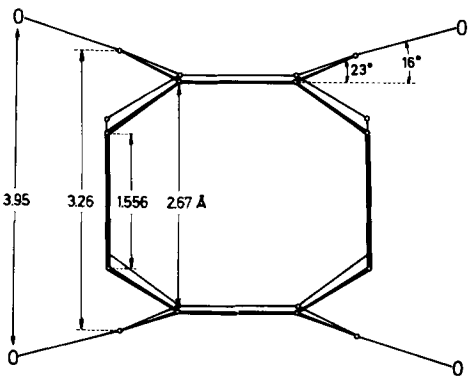
Subsequent synthetic steps were performed according to the preparation of the unsubstituted [2.2.2.2](1,2,4,5)cyclophane[2] with a number of modifications required by the special steric situation in the highly substituted [2.2]paracyclophane: chloromethylation of *(7)* (chloromethyl methyl ether, aluminum chloride) gave the bis(chloromethyl) compound *(8)*[5] (dec. >235 °C, 52 %) whose reduction with diisobutylaluminum hydride (boiling ether, 4 h) and subsequent oxidation with active manganese dioxide (ether, 50 h, 20 °C) led to 4,7-diformyl-12,15-dimethyl-5,8,13,16-tetramethoxy[2.2]paracyclophane *(9)*[5] (yellow needles, dec. >235 °C, 28 % yield); the bis(tosylhydrazone) of *(9)* underwent a carbenoid insertion reaction (sodium methoxide, tetrahydrofuran, 24 h irradiation with a 300-W daylight lamp, 29 %) to give tetramethoxy-[2.2.2.2](1,2,4,5)cyclophane *(10)*[5]: colorless prisms, m.p. 309—310 °C (dec.); MS, M^+ calc. for $C_{24}H_{28}O_4$ 380.1987, exp. 380.1985; ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 3.388$ (12H, CH_3O), AA'BB' (16H) with $\delta_A = 3.216$, $\delta_B = 2.724$, $J_{AB} = -13.0$, $J_{AA'} = 11.0$, $J_{AB'} = 3.6$, $J_{BB'} = 11.0$ Hz. The electron-rich cyclo-

phane *(10)* can be oxidized by lead(IV) acetate in trifluoroacetic acid to a radical cation, for which the splitting of the ESR signals corresponds to equivalent coupling of the radical electron with the protons of both cyclophane halves[7].



(10) *(11)*

Demethylation with methylmagnesium iodide[4], which has proved of value for synthesis of cyclophane quinones, proceeded with surprising ease (20 min, 180 °C) in spite of the potential difficulties envisaged at high temperatures owing to the considerable ring strain in *(10)*[8]. After oxidation with silver(I) oxide (acetone, 20 °C) we obtained the bisquinone *(11)*[5] in 42 % yield: yellow needles, dec. >305 °C; MS, M^+ calc. for $C_{20}H_{16}O_4$ 320.1049, exp. 320.1050; ^{1}H-NMR (80 MHz, $CDCl_3$) AA'BB' with $\delta_A = 3.007$, $\delta_B = 2.548$, $J_{AB} = -13.1$, $J_{AA'} = 11.4$, $J_{AB'} = 3.7$, $J_{BB'} = 11.4$ Hz. In contrast to other paracyclophane bisquinones with pseudogeminal orientation of the quinone units[9], double intramolecular cycloaddition of the two pairs of quinonoid C=C double bonds could not be accomplished photochemically in spite of their parallel arrangement and short distance. This might be connected with the strong boatlike deformation of the quinone units: X-ray structure analysis of *(11)*[10] shows the interplanar distances between the planes formed by the four bridged ring C atoms each to be 2.67 Å; the C—C(=O)—C planes deviate outwards from this plane by 23°:



Relatively stable radical anions are obtained from *(11)* by treatment with potassium *tert*-butoxide in dimethyl sulfoxide. The ESR spectrum shows the expected coupling of two groups of eight equivalent protons ($a_1 = 1.40$, $a_2 = 0.505$ G) expected for equivalence of the two cyclophane halves.

Catalytic hydrogenation of *(11)* (1 equiv. of hydrogen, 10 % Pd on activated charcoal, dioxane, 15 min, 20 °C) gave the quinhydrone *(1)*: black-violet microcrystals (from dioxane), dec. >300 °C, 60 % yield; MS, M^+ calc. for $C_{20}H_{18}O_4$ 322.1209, exp. 322.1205. In the ^{1}H-NMR spectrum (360 MHz, D_6-DMSO, 80 °C), ABCD multiplets ($\delta \approx 3.2$, 2.9, 2.6, 2.3) are observed for the four groups of four equivalent protons of the methylene bridges, together with the OH absorption at $\delta = 7.81$; on raising the temperature (to 140 °C) no evidence was found for fast exchange of oxidation states between the two halves of the molecule, as has been deduced for the pseudogeminal [2.2]paracyclophane quinhydrone[4].

Between 650 and 350 nm, the UV/VIS spectrum of *(1)* shows a broad intense charge transfer absorption at $\lambda_{max} = 491$ nm ($\varepsilon = 1280$, in methanol). The great similarity in line shape and position to the CT absorption of pseudogeminal [2.2]paracyclophane quinhydrone ($\lambda_{max} = 492$ nm, $\varepsilon = 1600$, in methanol)[4] appears surprising in view of the shorter transannular distances and the completely rigid mutual fixation of the donor and acceptor by fourfold bridging.

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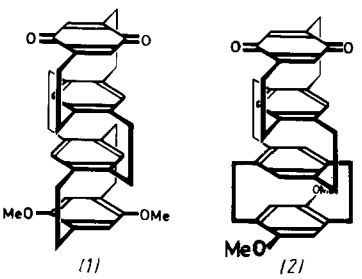
CAS Registry numbers:
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[3] *A. W. Hanson*, Acta Crystallogr. *B33*, 2003 (1977).
[4] *H. A. Staab, W. Rebafka*, Chem. Ber. *110*, 3333 (1977).
[5] Elemental analyses, mass spectra, and other spectroscopic properties are in agreement with the structures given.
[6] Cf. *J. Bruhin, W. Jenny*, Tetrahedron Lett. *1973*, 1215; *V. Boekelheide, I. D. Reingold, M. Tuttle*, J. Chem. Soc. Chem. Commun. *1973*, 406.
[7] *F. A. Neugebauer, V. Schwendemann, H. A. Staab*, unpublished.
[8] Compare the calculation of a strain energy of 49 kcal/mol for unsubstituted [2.2.2.2](1,2,4,5)cyclophane: *H. J. Lindner*, Tetrahedron *32*, 753 (1976).
[9] *H. Irngartinger, R.-D. Acker, W. Rebafka, H. A. Staab*, Angew. Chem. *86*, 705 (1974); Angew. Chem. Int. Ed. Engl. *13*, 674 (1974); *H. A. Staab, C. P. Herz, ibid. 89*, 839 (1977) and *16*, 799 (1977), respectively.
[10] *C. Krieger*, unpublished.

Indirect Donor-Acceptor Interactions in Quinhydrones of Quadruple-Layered [2.2]Paracyclophanes[1]

By *Heinz A. Staab* and *Udo Zapf* [*]

We have recently demonstrated for intramolecular quinhydrones of the triple-layered [2.2]paracyclophane system[2] that typical charge-transfer (CT) absorptions can also be observed when the donor and the acceptor are not in direct spatial contact but are separated by an aromatic π-electron system intercalated between the donor and acceptor moieties. Higher members of this class of compounds having additional aromatic π-electron systems inserted parallel between the donor and the acceptor are of interest in order to determine the range of indirect charge transfer of this kind. We now report the synthesis and spectroscopic properties of the intramolecular quinhydrones *(1)* and *(2)* having the donor and acceptor moieties in the external positions of a quadruple-layered [2.2]paracyclophane.

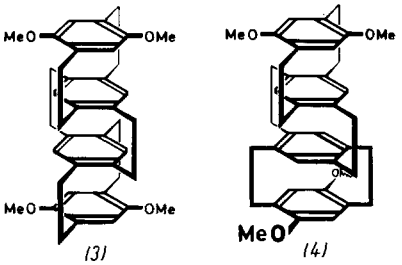


(1) *(2)*

pseudo-*ortho*-4,7-Dimethoxy-12-methyl-15-trimethylammoniomethyl[2.2]paracyclophane bromide[2] can be trans-

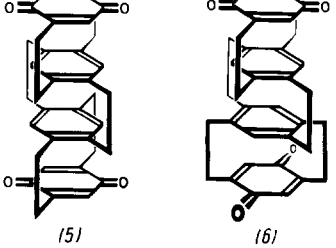
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formed in 20 % yield by 1,6-Hofmann elimination (conversion into the hydroxide with silver oxide/water; 12 hours' heating in boiling xylene with a water separator, addition of phenothiazine) into a mixture of diastereomeric quadruple-layered tetramethoxy[2.2]paracyclophanes *(3)* and *(4)* (ratio of 1:2). The diastereomers could be separated by repeated fractional crystallization from toluene/acetone (2:3): *(3)*[3] forms colorless platelets (from acetone), dec. >265°C; MS, M^+ calc. for $C_{40}H_{44}O_4$ 588.3239, exp. 588.3243; mass spectrometric fragmentation corresponds to the [2.2]paracyclophane structure: $m/e = 588$ (M^+, 80 %), 424 (40 %), 294 (100 %); ^{1}H-NMR (80 MHz, C_6D_6): $\delta = 2.1$—3.6 (m, 24H), 3.31 (s, 12H), 5.45 (s, 4H), 5.53 (s, 4H). *(4)*[3] is obtained from its acetone solution as colorless needles of m.p. 263—265°C (dec.); MS, M^+ exp. 588.3243, $m/e = 588$ (M^+, 100%), 424 (46%), 294 (97%); ^{1}H-NMR (80 MHz, C_6H_6): $\delta = 2.1$—3.6 (m, 24H), 3.28 (s, 12H), 5.46 (s, 4H), 5.68 (s, 4H). Assignment of *(3)* and *(4)*, and hence also that of the derived compounds *(5)*/*(1)* and *(6)*/*(2)*, is based on the crystal structure of *(3)*, which requires a molecular center of symmetry for this diastereomer[4].



(3) *(4)*

Demethylation of *(3)* and *(4)* was accomplished with methylmagnesium iodide[5] (5 equiv., 3h, 130—140°C, under nitrogen). After oxidation with silver(I) oxide (acetone, 1 h), chromatography (silica gel plates, chloroform) gave three fractions: $R_F \approx 0.57$, 50—70 % of the colorless compounds *(3)* and *(4)* recovered; $R_F \approx 0.44$, 4—8 % yield (*ca.* 15 % based on reacted *(3)* and *(4)*) of the red quinhydrone dimethyl ethers *(1)* and *(2)*; $R_F \approx 0.31$, 4—8 % yield of the orange-red bisquinones *(5)* and *(6)*: light red crystals (from ethanol), dec. 270°C; ^{1}H-NMR (80 MHz, C_6D_6) for *(5)*, $\delta = 1.3$—3.1 (m, 24H), 5.36 (s, 4H), 5.42 (s, 4H); for *(6)*, $\delta = 1.4$—3.1 (m, 24H), 5.35 (s, 4H), 5.48 (s, 4H). The UV/VIS spectra show intense longwave absorption bands [*(5)*, $\lambda_{max} = 415$ nm ($\varepsilon = 4960$); *(6)*, $\lambda_{max} = 417$ nm ($\varepsilon = 5010$), in chloroform] which are to be interpreted as CT absorptions of the donor-acceptor partial systems in *(5)* and *(6)*[6].



(5) *(6)*

The intramolecular quinhydrones *(1)* and *(2)* were further purified by chromatography on alumina from toluene and recrystallization. *(1)*[3], dark-red platelets (from methylcyclohexane), dec. >270°C; MS, M^+ calc. for $C_{38}H_{38}O_4$ 558.2770, exp. 558.2769; ^{1}H-NMR (80 MHz, C_6D_6) $\delta = 1.4$—3.5 (m, 24H), 3.28 (s, 6H), 5.41 (s, 4H), 5.47 (s, 4H).—*(2)*[3], dark-red crystals (from *n*-hexane), dec. >270°C; MS, M^+ exp. 558.2768; ^{1}H-NMR (80 MHz, C_6D_6) $\delta = 1.4$—3.55 (m, 24H), 3.27 (s, 6H), 5.38 (s, 2H), 5.43 (s, 2H), 5.57 (s, 2H), 5.61 (s, 2H).

The UV/VIS spectra of *(1)* and *(2)* show an intense CT absorption in the 350 to 550 nm range [*(1)*, $\lambda_{max} = 447$ nm ($\varepsilon = 2500$); *(2)*, $\lambda_{max} = 450$ nm ($\varepsilon = 2490$)]; their concentration independence (examined between about 7×10^{-4} and 8×10^{-6} M) confirms their intramolecular character. Not only are the intensities of the CT bands of *(1)* and *(2)* higher in comparison with the corresponding triple-layered [2.2]paracyclophane quinhydrones[2], but they also show a distinct bathochromic shift, indicating overall enhancement of the donor strength of the π-electron system interacting with the acceptor *p*-benzoquinone moiety in *(1)* and *(2)*. As in the case of the "triple-decker" quinhydrones[2], there is no evidence in the stereomeric pair *(1)*/*(2)* for any dependence of the CT band on the mutual orientation of the donor and acceptor units of the kind observed for simple [2.2]- and [3.3]paracyclophane quinhydrones[5, 7].

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CAS Registry numbers:
(1), 67688-39-5; *(2)*, 67737-42-2; *(3)*, 64519-28-4; *(4)*, 64425-59-8; *(5)*, 67688-40-8; *(6)*, 67737-43-3

[1] Charge-Transfer Interactions, Part 18. Part 17: *H. A. Staab, V. Schwendemann*, Angew. Chem. *90*, 805 (1978); Angew. Chem. Int. Ed. Engl. *17*, 756 (1978).

[2] *H. A. Staab*, Lecture ISNA III, San Francisco, California, 22. 8. 1977; *H. A. Staab, U. Zapf, A. Gurke*, Angew. Chem. *89*, 841 (1977); Angew. Chem. Int. Ed. Engl. *16*, 801 (1977).—These results have meanwhile been confirmed by *H. Machida, H. Tatemitsu, Y. Sakata, S. Misumi* [Tetrahedron Lett. *1978*, 915].

[3] Elemental analyses, mass spectra, and other spectroscopic properties are in agreement with the structures given.

[4] *(3)* forms monoclinic crystals, $a = 8.31$, $b = 21.35$, $c = 9.32$ Å, $\beta = 106°$; space group $P2_1/c$; $Z = 2$ (*C. Krieger*, unpublished).

[5] *H. A. Staab, W. Rebafka*, Chem. Ber. *110*, 3333 (1977).

[6] Cf. *D. J. Cram, A. C. Day*, J. Org. Chem. *31*, 1227 (1966); *H. Tatemitsu, T. Otsubo, Y. Sakata, S. Misumi*, Tetrahedron Lett. *1975*, 3059.

[7] *H. A. Staab, C. P. Herz*, Angew. Chem. *89*, 839 (1977); Angew. Chem. Int. Ed. Engl. *16*, 799 (1977).

A Novel Photochemical Synthesis of Propellanes[**]

By *Gerd Kaupp* and *Michael Stark*[*]

Hitherto, the photochemical syntheses of propellanes[1] utilized intramolecular [2+2]-[1, 2], [4+2]-[1] and [4+4]-cycloadditions[3] or trapping reactions of doubly-bridged electronically excited conjugated alkenes with simple alkenes[1, 4]. We have now been able to trap electronically excited acyclic chromophores with bicyclic alkenes to give propellanes.

Mechanistic findings with [2+2]-photocycloadditions of *trans*-stilbene *(1)* and diphenylacetylene *(5)*[5] suggested that *(1*)* and *(5*)* are more effectively trapped by bicycloalkenes with doubly-bridged double bonds to give propellanes than by simple cycloalkenes to give bicyclic [2+2]-adducts. Thus, in the readily accessible tetrahydroindene *(2)*[6] the (electron-rich) central double bond ought to preferably react with *(1*)* or *(5*)*. Since molecular models indicate that steric hindrance of the chemically productive collision of these partners is not excessive, propellane formation ought also to compete with the substituting additions[7] favored here [to give *(4)* and *(7)*, respectively]. These predictions could in fact be confirmed by the ready syntheses of *(3)* and *(6)* (Table 1).

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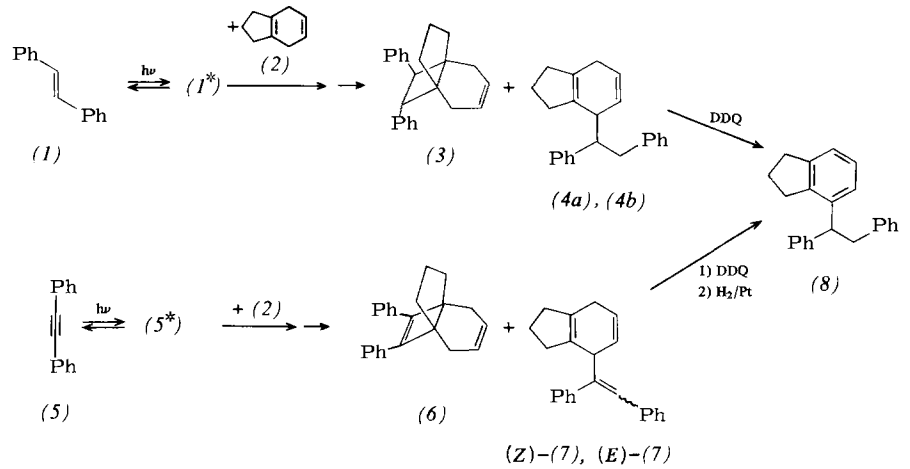


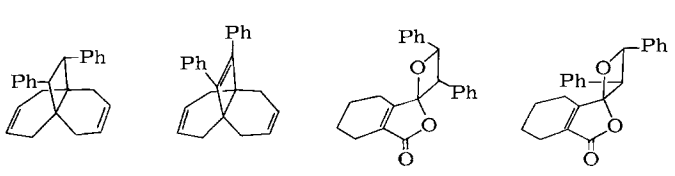
Table 1. Properties of *(3)*, *(6)*, *(8)*, *(9)*, and *(10)*. All the compounds gave the correct elemental analysis.

	M.p. [°C]	^{1}H-NMR (90 MHz, CCl_4, δ)	UV (CH_3CN) [nm] (logε)
(3) [a]	76	7.3—6.9 (10H, m), 6.0—5.5 (2H, m), 3.77 (1H, AB, J=10.5 Hz, $\Delta\nu_{1/2}$=3.5 Hz), 3.51 (1H, BA, $\Delta\nu_{1/2}$=2 Hz), 2.51 (1H, dd, J=16, 6 Hz), 2.15—1.1 (9H, m)	
(6) [b]	79	7.5—6.95 (10H, m), 5.9—5.6 (2H, m), 2.7—2.35 (2H, m), 2.2—1.5 (6H, m), 1.5—1.0 (2H, m)	226 (4.23), 286 (4.02), 293 (sh, 4.01), 310 (sh, 3.93), 330 (sh, 3.59)
(8)		7.2—6.75 (13H, m), 4.14 (1H, t, J=7.5 Hz), 3.22 (2H, d, J=7.5 Hz), 2.77 (2H, t, J=7 Hz), 2.50 (2H, t, J=7 Hz), 1.83 (2H, quin., J=7 Hz)	
(9)	122	7.3—6.9 (10H, m), 5.95—5.5 (4H, m), 3.89 (2H, s), 2.23 (2H, dAB, J=16.5, 5.5 Hz), 1.99 (2H, br. AB, J=16.5 Hz), 1.88 (2H, dBA), 1.64 (2H, br. BA, $\Delta\nu_{1/2}$ *ca.* 7 Hz)	
(10) [c]	85	7.25—6.95 (10H, m), 5.9—5.55 (4H, m), 2.35 (4H, br. AB, J=16 Hz, $\Delta\nu_{1/2}$ ca. 9 Hz), 2.08 (4H, br. BA, $\Delta\nu_{1/2}$=3.5 Hz)	226, 268 (sh), 275, 283 (sh), 294 (sh), 310 (sh), 332 (sh)

[a] ^{13}C-NMR (90.5 MHz, $CDCl_3$): δ=141.5, 140.6 (quart. arom. C), 129.4, 127.4 (olefin. C), 128.1, 128.0, 127.8, 127.0 (*o*-, *m*-arom. C), 125.9, 125.7 (*p*-arom. C), 50.8, 49.4 (bridgehead-C), 46.9, 45.3 (benzyl. C), 41.7, 37.2, 35.1, 30.3, 24.9 (allyl. and aliph. C). [b] Fluorescence (cyclohexane): λ_{max}^{corr}=380 nm, Φ_{fl}=0.60. [c] Fluorescence (cyclohexane): λ_{max}^{corr}=380 nm.

Selective irradiation ($\lambda > 290$ nm) of *(1)* dissolved in *(2)* affords 56 % of the [4.3.2]propellane *(3)* and 21 % of a diastereomeric mixture of *(4a)* and *(4b)*, together with traces of 1,2-diphenylethane and higher molecular weight material[8].

Correspondingly, irradiation of *(5)* in *(2)* (almost selective excitation, λ=253.7 nm) affords mainly the [4.3.2]propellane *(6)* (41 %), together with (*Z*)-*(7)*, (*E*)-*(7)*, unreacted *(5)*, three unknown products (none of which showed fluorescence in the visible range), and photolysis products of *(5)*[8, 9].



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

The utility of this versatile method for the synthesis of substituted propellanes having different numbers of double bonds is not restricted to tetrahydroindene. Thus, reaction of 1,4,5,8-tetrahydronaphthalene with *(1*)* or *(5*)* affords the [4.4.2]propellanes *(9)* (35%) and *(10)* (37%) (Table 1). However, "electron-poor" doubly bridged alkenes apparently do not react with *(1*)* and *(5*)* to give propellanes. For example, reaction of 3,4,5,6-tetrahydrophthalic anhydride with *(1*)* leads to the spirooxetanes *(11)* (40%; m.p. 143 °C) and *(12)* (13%; m.p. 154 °C)[10].

Experimental

trans-10,11-Diphenyltricyclo[4.3.2.0^{1,6}]undec-3-ene *(3)*: A solution of *(1)* (2.0 g, 11.1 mmol) in *(2)* (50 g, 0.42 mol) is irradiated under N_2 at 25 °C for 12 h with a mercury high-pressure lamp (Hanau, Q 81) using a pyrex filter. After removal of excess *(2)* by distillation the residue is chromatographed on 200 g SiO_2 with cyclohexane as eluent. Initially, 1.89 g (56 %) *(3)* with 40 mg (2 %) 1,2-diphenylethane is eluted [crystallization from ethanol (5 ml) furnishes 1.78 g (53%) *(3)*, m.p. 76 °C] and finally 690 mg (21 %) of a 3:2 mixture of the diastereomers *(4a)*, *(4b)* [^{1}H-NMR analysis[10]; separation by preparative thin-layer chromatography on SiO_2 with cyclohexane]. The mixture of diastereomers is heated under reflux with 550 mg (2.4 mmol) DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) in 30 ml benzene for 3 h under N_2. After filtration over 30 g SiO_2 with cyclohexane, *(8)* is purified by preparative thin-layer chromatography (SiO_2/cyclohexane) and short-path distillation (5×10^{-4} torr; bath temp. 100 °C); yield 0.52 g (75%).

10,11-Diphenyltricyclo[4.3.2.0^{1,6}]undeca-3,10-diene *(6)*: A solution of *(5)* (2.0 g, 11.1 mmol) in *(2)* (20 g, 0.17 mol) is irradiated in a quartz tube for 4 d with eight mercury low-pressure lamps (253.7 nm) in a Rayonet reactor at 30 to 35 °C (after 2 d the solution is transferred to a fresh quartz tube because of deposition of polymeric products). The excess of *(2)* is removed by distillation at 40 °C under vacuum and the oily residue is chromatographed on 200 g SiO_2 with cyclohexane. On treatment of the residue of the first eluate (300 ml after 700 ml forerun) with ethanol (10 ml) at −20 °C, there separates out 1.13 g (34%) of *(6)* (m.p. 79 °C). According to gas chromatographic analysis (1% SE 30, 2m, 210 °C) the mother liquor and the second eluate (500 ml) contain 0.23 g (7%) *(6)*, 0.60 g (18%) (*Z*)-*(7)*, 0.30 g (9%) (*E*)-*(7)*, 0.26 g (13%) *(5)*, and three other compounds (together, *ca.* 5%). (*Z*)-*(7)* and (*E*)-*(7)* were separated from the mixture for ^{1}H-NMR analysis[10] by preparative thin-layer chromatography (SiO_2/cyclohexane). For isolation of *(8)* the mixture is treated, as above, with DDQ and then hydrogenated catalytically with PtO_2 in ethyl acetate; yield after preparative TLC = 0.48 g.

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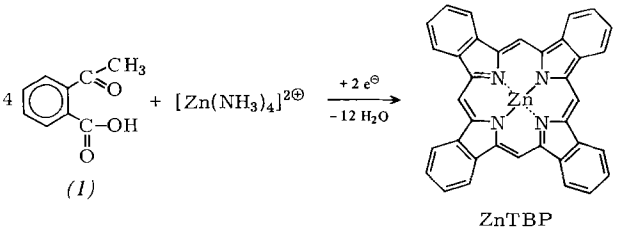
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[2] *G. Kaupp*, Angew. Chem. *83*, 361 (1971); Angew. Chem. Int. Ed. Engl. *10*, 340 (1971); references cited therein; *C. W. Shoppee, Y.-s. Wang*, J. Chem. Soc. Perkin Trans. I *1976*, 695; *H. A. Staab, C. P. Herz*, Angew. Chem. *89*, 839 (1977); Angew. Chem. Int. Ed. Engl. *16*, 799 (1977).
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[4] Ref. [3b], p. 405f.; *H.-M. Hutmacher, H.-G. Fritz, H. Musso*, Angew. Chem. *87*, 174 (1975); Angew. Chem. Int. Ed. Engl. *14*, 180 (1975); *B. Deppisch, H.-G. Fritz, I. Schneider, H. Musso*, Chem. Ber. *111*, 1497 (1978).
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[7] Reviews: see [3b], p. 278ff.; 360ff.; intramolecular examples: *G. Kaupp*, Angew. Chem. *90*, 161 (1978); Angew. Chem. Int. Ed. Engl. *17*, 150 (1978).
[8] Paper presented at the Chemiedozententagung in Berlin, April 4, 1978.
[9] Cf. [3b], p. 462f.
[10] *G. Kaupp, M. Stark*, unpublished results; we are indebted to Prof. *H. Fritz*, CIBA-GEIGY AG, CH-4002 Basel, for the recording of NMR spectra.

Simple Template Synthesis of Zinc Tetrabenzporphyrin[**]

By *Arnd Vogler* and *Horst Kunkely*[*]

Although tetrabenzoporphyrin (TBP) and some of its metal complexes had already been synthesized some 40 years ago by *Helberger et al.* and *Linstead et al.*[1], very little is known about its chemical and physical properties[2]. The main reasons for this are that the previously published methods for the synthesis of TBP are extremely complicated and the yields are very low[2]. The few investigations so far carried out on TBP have been concerned almost exclusively with the unusual optical properties[2] of this pigment. ZnTBF, for example, exhibits three different luminescences. A study of the redox behavior of TBP complexes could make an important contribution to our understanding of electron transfer by metalloporphyrins (*e.g.* cytochromes) in biological systems. The redox potentials of porphyrins could hitherto be altered essentially only by varying the central metal and additional axial ligands[3]. The greatly expanded π-electron system of TBF should allow reductions and oxidations at comparatively low potentials.

We report here on a single-step template synthesis of ZnTBP, which enables a detailed investigation of TBP and its metal complexes. The synthesis involves heating a solution of commercially available 2-acetylbenzoic acid ("acetophenone-2-carboxylic acid") *(1)* and zinc acetate in aqueous ammonia in the presence of a molecular sieve; the stoichiometry is as shown in the following scheme:



The two electrons required for the reduction could originate from the acetate ion or from decomposition products of excess acid *(1)*. The readily purifiable crude ZnTBP contains no tetrabenzoazaporphyrins which often occur as by-products in the previously described syntheses and which are difficult to separate. ZnTBP was identified by elemental analysis and by IR and UV/VIS spectra[2]. The electron absorption spectrum[2] is especially valuable for detecting the presence of impurities. Demetalation of ZnTBP leads to the protonated form $TBPH_2$[4] which can be used as starting material for the preparation of other complexes[5].

Procedure

To a solution of 20 g of *(1)* (Ega/Aldrich), 30 g zinc acetate, and 1 g sodium hydroxide in 130 ml conc. ammonia in a 2 l flask is added 10 g of molecular sieve (4 Å, Merck) and the mixture rapidly heated under a stream of nitrogen. Rapid heating is achieved by transferring the flask and contents to a fully pre-heated mantle (G2/2). Within a short time an almost black residue is obtained whose temperature reaches about 400 °C. After about 1.5 h the residue is allowed to cool, with continued passage of N_2, and then extracted several times each with 100 ml of hot pyridine. The combined extracts are cooled, treated with 2 l ether, allowed to stand for 1 h, and filtered. The dark-green filtrate is concentrated to about 30 ml in a rotating evaporator and then treated with 150 ml ether. This solution is chromatographed on Al_2O_3 (neutral), using a 20 % solution of pyridine in ether as eluent. The tailings, which contain impurities (absorption bands at 460 nm), are discarded. The eluate is concentrated to 10 ml by evaporation, treated with 100 ml methanol, and then allowed to stand for *ca.* 12 h at −20 °C. The precipitate—shiny, dark violet crystals—is filtered off, washed with ice-cold methanol, then with petroleum ether, and finally dried; yield 2.9 g (17 %).

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CAS Registry numbers:
(1), 577-56-0; ZnTBP, 14586-52-8; $[Zn(NH_3)_4]^{2+}$, 17095-57-7

[1] For a review of all previously reported syntheses of TBP see [2].
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[5] *J. W. Buchler* in *K. M. Smith:* Porphyrins and Metalloporphyrins. Elsevier, New York 1975, Chap. 5.

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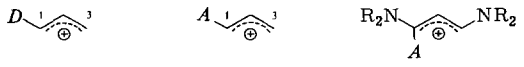
Acceptor-Substituted Allyl Cations as Ambifunctional Electrophiles[1]

By *Rudolf Gompper* and *Rainer Sobotta*[*]

In continuation of our studies on the influence of substituents on the reactions of ambifunctional anions, we have applied the allopolarization principle[2] to allyl cations. On

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the basis of the charge distribution (HMO model), 1-donor substituted cations are accordingly expected to react preferentially at C-1 with nucleophiles (this is substantiated by several examples), whereas 1-acceptor substituted cations *(2)* should

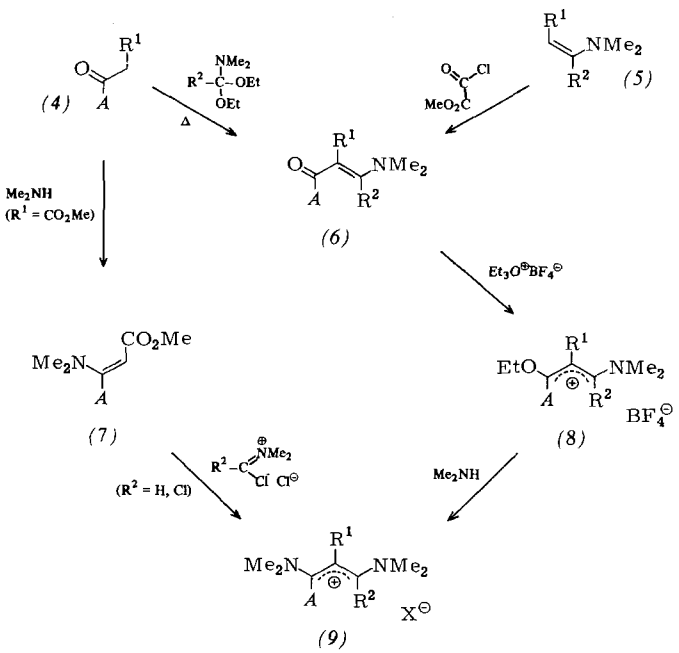


(1) *(2)* *(3)*

$1^{\oplus}_1 > 1^{\oplus}_3$ $1^{\oplus}_3 > 1^{\oplus}_1$

react at C-3. The reactions of *(2)* did not appear to be a very promising field of study because the simple salts of these cations are probably unstable. We therefore turned our attention to the allyl cations *(3)* having a charge distribution corresponding to that of *(2)*; their stability is expected to resemble that of *(1)*.

Salts of type *(9)* containing the partial structure *(3)* can be obtained from *(4)* or *(5)* *via* reactions known from the chemistry of vinamidinium salts[3], β-aminovinyl ketones[4], and enamines[5]: reactions of *(4)* with amide acetals to give



Scheme 1. Synthesis of compounds *(6)* and *(9)*.

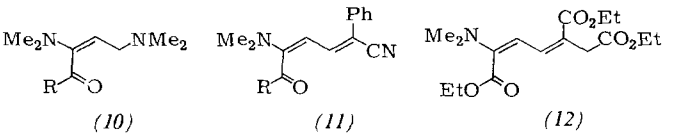
(6) (only the action of DMF acetal on several 1,2-propanediones was previously known[6]) or of *(5)* with oxalic ester chloride to give *(6)*, of *(6)* with triethyloxonium tetrafluoroborate to form *(8)*, and then with dimethylamine to form *(9)*, and of *(7)* with amidoyl chlorides which likewise gives *(9)* (see Scheme 1 and Table 1).

Table 1. 1-Acceptor substituted β-aminovinyl ketones *(6)* and vinamidinium salts *(9)*, X = ClO_4.

	A	R^1	R^2	*(6)* M.p. [°C] B.p. [°C/torr]	*(9)* M.p. [°C]
a	CO_2Et	H	H	38	104—105
b	CO_2Et	H	Me	170/0.1	oil
c	CO_2Me	Me	H	81—82	—
d	CO_2Me	H	Ph	250 [a]	129—131 [a]
e	CO_2Et	Ph	H	63—64	oil
f	CO_2Me	H	NMe_2	80—83	98—100
g	CO_2Et	CO_2Et	H	—	129
h	CO_2Me	CO_2Me	H	—	105—106
i	CO_2Me	CO_2Me	Cl	—	115—117
j	COPh	H	H	92—93	148—150
k	COPh	H	Me	119—120	—
l	COPh	Me	H	90—92	—
m	COPh	Ph	H	oil [6]	—
n	$CH(OMe)_2$	H	H	150/0.1	90—92

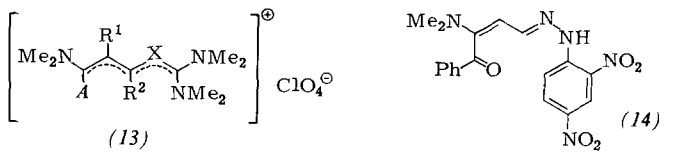
[a] R_2N = Morpholino.

The salts *(9)* are resistant to hydrolysis at room temperature. Reactions of *(9a)* and *(9j)* with $NaBH_4$ in ethanol, leading to *(10a)* (colorless oil) and *(10b)* (yellow oil), demonstrate the expected relationship between the regioselectivity and charge distribution in compounds of type *(2)*. The formation of *(11a)* and *(11b)* from *(9a)* and *(9j)*, respectively, and benzyl cyanide (Na ethoxide in ethanol), of *(12)* from *(9a)* and diethyl succinate (NaH, THF), of *(14)* from *(9j)* and 2,4-dinitrophenylhydrazine, and of *(13a)*—*(13d)* from *(9a)*, *(9h)*, *(9i)*, and *(9j)*, respectively, on heating with 1,1-bis(dimethylamino)ethylene in DMSO, DMF, or dichloromethane, as well as that of *(13e)* and *(13f)* from *(9a)* and *(9i)*, respectively, and tetramethylguanidine could also be subject to thermodynamic control (see Scheme 2 and Table 2).



(10) *(11)* *(12)*

(a), R = OEt; *(b)*, R = Ph



(13) *(14)*

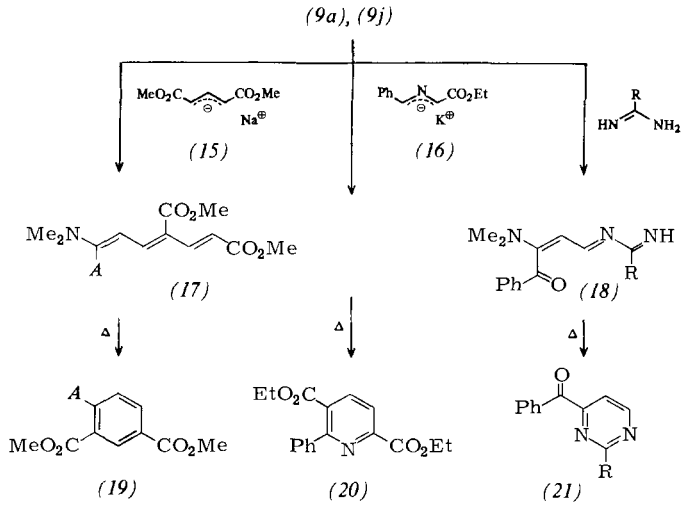
Scheme 2. Open chain reaction products of compounds *(9)*. *(10a)*, b.p. 115°C/0.1 torr. ^{1}H-NMR ($CDCl_3$): $\delta = 1.36$ (t, 3H), 2.26 (s, 6H), 2.63 (s, 6H), 3.03 (d, 2H), 4.30 (q, 2H), 4.70 (t, 1H); *(10b)*, b.p. 150°C/0.1 torr; *(11a)*, m.p. 64—66°C; *(11b)*, m.p. 138—139°C; *(12)*, b.p. 190°C/0.1 torr; *(13)* see Table 2; *(14)*, m.p. 163—165°C.

Table 2. Acceptor-substituted salts *(13)*.

	A	R^1	R^2	X	*(13)*, m.p. [°C]
a	CO_2Et	H	H	CH	128—132
b	CO_2Me	CO_2Me	H	CH	124—126
c	CO_2Me	CO_2Me	NMe_2	CH	164—167
d	COPh	H	H	CH	173—175
e	CO_2Et	H	H	N	55—56
f	CO_2Me	CO_2Me	NMe_2	N	145—147

The preparative significance of the salts *(9)* is further demonstrated by reactions resembling the aromatic synthesis described by *Jutz*[3c] which lead to (hetero)aromatic carboxylic acids and ketones: reaction of *(9a)* and *(9j)* with *(15)* initially gives the hexatrienes *(17a)* and *(17b)*, respectively, which are transformed into the benzenecarboxylic esters *(19a)* and *(19b)* on heating in xylene. The primary product obtained upon the action of *(16)*[7] on *(9a)* affords the pyridinedicarboxylic ester *(20)* on bulb-to-bulb distillation. Compound *(9a)* reacts with amidines to form *(18a)* and *(18b)*, from which the pyrimidines *(21a)* and *(21b)* result on heating (see Scheme 3).

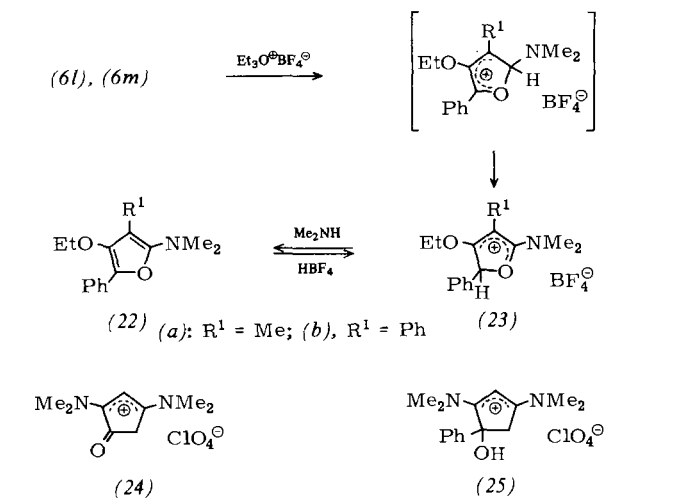
The action of triethyloxonium tetrafluoroborate on *(6l)* and *(6m)* does not give the salts of the allyl cations *(8l)* and *(8m)*, respectively, but instead the furanium salts *(23a)* and *(23b)*, which form the furans *(22a)* (49%, orange-yellow



(a), A = CO_2Et; *(b), A* = COPh *(a),* R = Me; *(b),* R = Ph

Scheme 3. Cyclic reaction products of compounds *(9)*. *(17a)*, m.p. 89°C; *(17b)*, m.p. 113—115°C; *(18b)*, m.p. 159°C; *(19a)*, b.p. 170°C/0.1 torr; *(19b)*, m.p. 116—118°C; *(20)*, m.p. 43°C; *(21a)*, b.p. 130°C/0.1 torr; *(21b)*, m.p. 81—83°C.

oil) and *(22b)* (36%, orange-red oil) with dimethylamine. HBF_4 regenerates *(23)* from *(22)*. Five-membered rings are



(22) (a): R^1 = Me; *(b)*, R^1 = Ph *(23)*

(24) *(25)*

Scheme 4. Cyclic reaction products of compounds *(6)* and *(8)*. *(22a)*, b.p. 115—120°C/0.1 torr; *(22b)*, b.p. 190°C/0.1 torr; *(23a)*, m.p. 103—105°C; *(24)*, m.p. 160—162°C; *(25)*, m.p. 161—162°C.

also obtained instead of *(9)* on treatment of *(8b)* and *(8k)* with an excess of dimethylamine. *(24)* (72%) and *(25)* are suitable precursors for donor-substituted cyclopentadienylium salts and cyclopentadienones.

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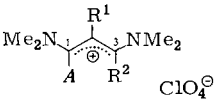
CAS Registry numbers:
(4a), 617-35-6; *(4c)*, 3952-66-7; *(4d)*, 600-22-6; *(4e)*, 6613-41-8; *(4g)*, 108-56-5; *(4h)*, 25007-54-9; *(4j)*, 579-07-7; *(4l)*, 3457-55-4; *(4m)*, 23464-17-7; *(4n)*, 6342-56-9; *(5a)*, 5763-87-1; *(5b)*, 22499-75-8; *(5c)*, 6163-56-0; *(5d)*, 14548-16-4; *(5e)*, 10448-42-7; *(5f)*, 815-62-3; *(5g)*, 924-99-2; *(5h)*, 999-59-7; *(5i)*, 67751-13-7; *(6a)*, 67751-14-8; *(6b)*, 67751-15-9; *(6c)*, 67751-16-0; *(6d)*, 67751-17-1; *(6e)*, 67751-18-2; *(6f)*, 67751-19-3; *(6j)*, 67751-20-6; *(6k)*, 67751-21-7; *(6l)*, 67751-22-8; *(6m)*, 36777-65-8; *(6n)*, 67751-23-9; *(7a)*, 67751-24-0; *(7c)*, 67751-25-1; *(7j)*, 67751-26-2; *(7n)*, 67751-27-3; *(8a)*, 67751-29-5; *(8b)*, 67751-31-9; *(8c)*, 67751-33-1; *(8d)*, 67751-35-3; *(8e)*, 67751-37-5; *(8f)*, 67751-39-7; *(8g)*, 67751-41-1; *(8h)*, 67751-43-3; *(8i)*, 67751-45-5; *(8j)*, 67751-47-7; *(8k)*, 67751-49-9; *(8l)*, 67751-51-3; *(8m)*, 67751-53-5; *(8n)*, 67751-55-7; *(9a)*, 67761-16-4; *(9b)*, 67761-59-5; *(9d)*, 67751-57-9; *(9e)*, 67751-59-1; *(9f)*, 67751-61-5; *(9g)*, 67751-63-7; *(9h)*, 67750-71-4; *(9i)*, 67750-73-6; *(9j)*, 67750-75-8; *(9n)*, 67761-61-9; *(10a)*, 67750-76-9; *(10b)*, 67750-77-0; *(11a)*, 67750-78-1; *(11b)*, 67750-79-2; *(12)*, 67750-80-5; *(13a)*, 67750-82-7; *(13b)*, 67750-84-9; *(13c)*, 67750-86-1; *(13d)*, 67750-88-3; *(13e)*, 67750-90-7; *(13f)*, 67750-92-9; *(14)*, 67750-93-0; *(15)*, 67750-94-1; *(16)*, 67750-95-2; *(17a)*, 67750-96-3; *(17b)*, 67750-97-4; *(18a)*, 67750-98-5; *(18b)*, 67750-99-6; *(19a)*, 67751-00-2; *(19b)*, 67751-01-3; *(20)*, 67751-02-4; *(21a)*, 67751-03-5; *(21b)*, 67751-04-6; *(22a)*, 67751-05-7; *(22b)*, 67751-06-8; *(23a)*, 67761-55-1; *(23b)*, 67761-57-3; *(24)*, 67751-08-0; *(25)*, 67751-10-4; amide acetal (R^2 = H), 1188-33-6; amide acetal (R^2 = Me), 19429-85-7; amide acetal (R^2 = Ph), 19429-87-9; amide acetal (R^2 = NMe), 67751-11-5; amide acetal (R^2 = Cl), 67751-12-6; oxalic ester chloride, 5781-53-3; amide chloride (R^2 = H), 3724-43-4; amide chloride (R^2 = Cl), 33842-02-3; dimethylamine, 124-40-3; benzyl cyanide, 140-29-4; diethyl succinate, 123-25-1; amidine (R = Me), 143-37-3; amidine (R = Ph), 618-39-3

[1] The Allopolarization Principle and Its Applications, Part 1. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.
[2] *R. Gompper, H.-U. Wagner*, Angew. Chem. *88*, 389 (1976); Angew. Chem. Int. Ed. Engl. *15*, 321 (1976).
[3] a) *H. Böhme, H. G. Viehe*, Adv. Org. Chem. 9 (1976); b) *D. Lloyd, F. H. McNab*, Angew. Chem. *88*, 496 (1976); Angew. Chem. Int. Ed. Engl. *15*, 459 (1976); c) *C. Jutz*, Fortschr. Chem. Forsch. *73*, 125 (1978).
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1,3-Bis(dimethylamino)vinylcarbene[1]

By *Rudolf Gompper* and *Rainer Sobotta*[*]

In compliance with the charge distribution in the allyl system, 1-acceptor substituted vinamidinium salts *(1)* preferentially react with nucleophiles at C-3[1]. However, the ambifunctional character of *(1)* also embraces the acceptor group



(1a), R^1 = R^2 = H; *A* = COPh
(1b), R^1 = R^2 = H; *A* = CO_2Et

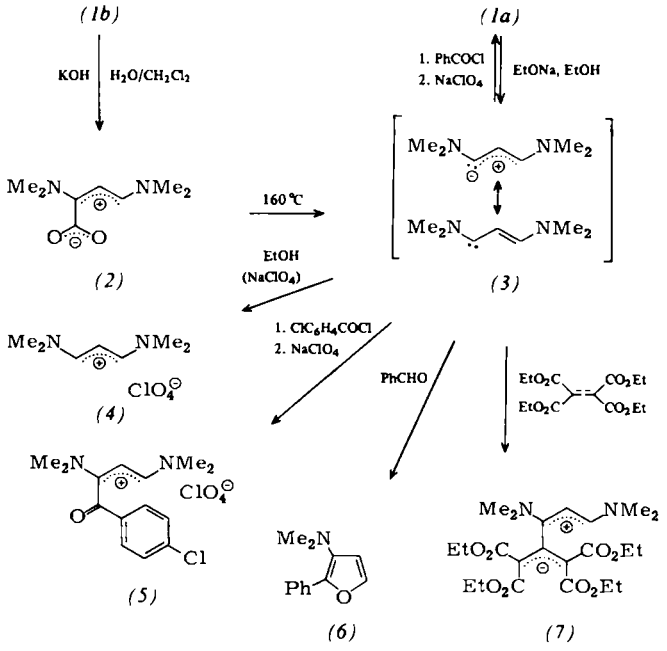
A: treatment of *(1a)* with Na ethoxide in ethanol leads exclusively to the salt *(4)* together with ethyl benzoate. The simplest explanation of this behavior invokes the intermediacy of the nucleophilic carbene *(3)*, which undergoes subsequent protonation. Analogous eliminations of acyl groups have been observed with 2-acyl-1-methylpyridinium salts[3]; the decarboxylation of 1-methylpyridinium-2-carboxylate[4] should also be mentioned in this context.

A detailed study of the reactions of the nucleophilic vinylcarbene *(3)* is facilitated by the possibility of generating the species from the zwitterion *(2)*, which is accessible by alkaline hydrolysis of *(1b)* (81%; colorless crystals; see Scheme 1).

Heating of *(2)* with an excess of benzoyl chloride or 4-chlorobenzoyl chloride to 160°C affords *(1a)*, or *(5)*, respectively, in 65—70% yield. Similar reaction with benzaldehyde gives the furan *(6)*.

The reaction of *(2)* with tetraethyl allenetetracarboxylate, leading to the zwitterion *(7)* (32%; yellow needles), is remarkable. The formation of *(7)* demonstrates that cyclopropanes do not necessarily result on reaction of carbenes with olefins (for further examples, see ref. [5]).

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Scheme 1. Generation of the vinylcarbene *(3)* and its reactions. *(2)*, m.p. 199—200 °C (dec.), IR (KBr): 1642, 1574, 1395, 1282 cm^{-1}, ^{1}H-NMR ($CDCl_3$/[D_6]-EtOH): $\delta = 3.15$ (s, 3H), 3.21 (s, 3H), 3.36 (s, 6H), 5.0 (d, 1H), 7.75 (d, 1H); *(4)*, m.p. 118 °C (120 °C [2]); *(5)*, m.p. 182 °C; *(6)*, b.p. 150 °C/0.15 mbar; *(7)*, m.p. 150—151 °C.

Cyclization of *(3)* to give 1,2-bis(dimethylamino)cyclopropene has not yet been observed, which is hardly surprising in view of the pronounced tendency of 1-dimethylamino-2,3-diphenylcyclopropene[6] and of dicarbonyl(cyclopentadienyl)(1,2,3-triphenylcyclopropenyl)iron[7] to undergo ring cleavage in the presence of acids.

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CAS Registry numbers:
(1a), 67750-75-8; *(1b)*, 67761-16-4; *(2)*, 67761-17-5; *(3)*, 67761-18-6; *(4)*, 1611-78-5; *(5)*, 67761-20-0; *(6)*, 67761-21-1; *(7)*, 67761-22-2; tetraethyl allene-tetracarboxylate, 67761-23-3

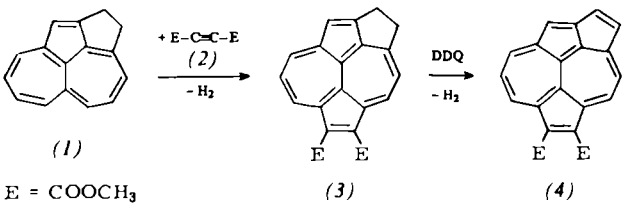
[1] The Allopolarization Principle and Its Applications, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 1: *R. Gompper, R. Sohotta*, Angew. Chem. *90*, 808 (1978); Angew. Chem. Int. Ed. Engl. *17*, 760 (1978).
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Synthesis of Penta- and Hexacyclic Conjugated Hydrocarbons by Cycloaddition Reactions[**]

By *Klaus Hafner, Hans Dieter Diesel*, and *Winfried Richarz*[*]

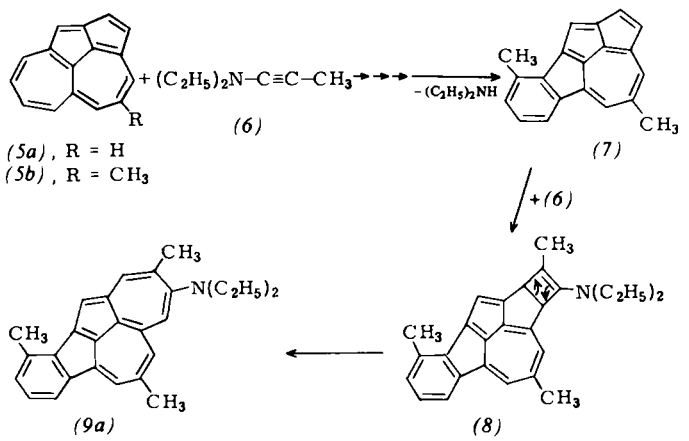
Cycloaddition reactions of bi- and tricyclically conjugated hydrocarbons such as pentalenes, azulenes, and aceheptylenes with electron-poor and electron-rich alkynes recently opened up an unexpectedly facile entry to cyclically conjugated systems[1]. On examining the scope and limitations of this synthetic approach we obtained, among other compounds, for the first time, the penta- and hexacyclic polyenes *(4)*, *(9a)*, and *(10)*.

By analogy with the dipolar cycloaddition of dimethyl acetylenedicarboxylate and aceheptylene leading to dimethyl 1,2-dicyclopenta[*ef,kl*]heptalenedicarboxylate[1c], the 2,3-ethano-bridged derivative of aceheptylene, 1,2-dihydropentaleno-[6.1.2-*def*]heptalene *(1)*[2], also reacts with the electron-poor alkyne *(2)* *via peri*-annelation of a five-membered ring to give 30% of the dihydropentaleno[6.1.2-*fgh*]aceheptylene derivative *(3)*[3] (yellow-brown rods, m.p. 176 °C). On dehydrogenation with 2,3-dichloro-5,6-dicyanoquinone (DDQ), *(3)* yields the first completely conjugated nonbenzenoid pentacyclic compound having an 18π-electron system, the ester *(4)*,



in 92% yield as brown rods of m.p. 164—165 °C. All attempts to synthesize *(4)* directly by cycloaddition of *(2)* and pentaleno[6.1.2-*def*]heptalene *(5a)*[2] have been unsuccessful so far.

In contrast, reaction of the methyl derivative *(5b)*[4] with *N,N*-diethyl-1-propynylamine *(6)* for 90 min in refluxing xylene affords the thermally stable pentacyclic 1,2-benzopentaleno[6.1.2-*def*]heptalene derivative *(9a)* in 34% yield (based on conversion of *(5b)*) as brown needles of m.p. 188 °C. Like aceheptylene[1c], *(5b)* is expected to initially undergo a dipolar cycloaddition with *(6)*. Two consecutive valence isomeriza-



tions and subsequent elimination of diethylamine lead to the pentacyclic hydrocarbon *(7)*. Like cyclopent[*cd*]azulene[1b], this product immediately combines in another formal [2+2] cycloaddition with a further mole of *(6)* to give *(8)*, which by valence isomerization finally yields *(9a)*. Even on reaction of *(5b)* with less than one equivalent of *(6)*, compound *(7)* could not be isolated. In accordance with quantum-chemical calculations[5] on the dicyclopent[*cd,ij*]azulene system present in *(7)*, this compound exhibits a pronounced reactivity towards cycloaddition partners, mainly at the double bond in the unsubstituted five-membered ring.

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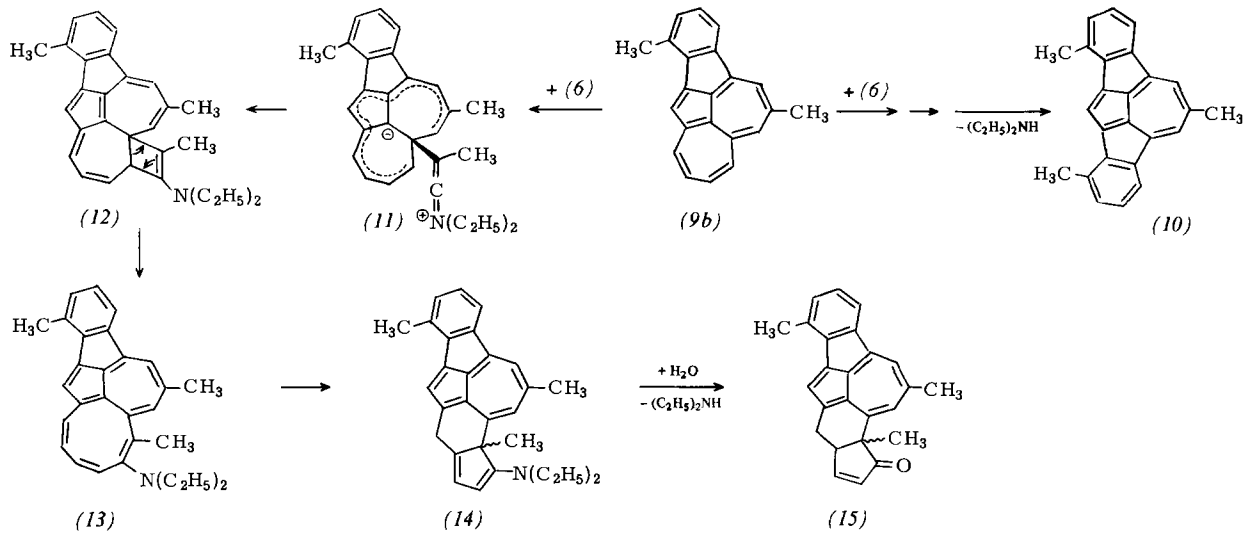


Table 1. Spectroscopic data of *(4)*, *(9a)*, *(10)*, and *(15)*.

Cpd.	^{1}H-NMR (δ, J) in $CDCl_3$	UV, λ_{max} [nm] (logε) in dioxane
(4)	4.14 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 7.19 (dd, J_1 = 10 Hz, J_2 = 1.5 Hz; 1H), 7.48 (d, J = 4.5 Hz; 1H), 7.58 (d, J = 4.5 Hz; 1H), 8.00 (d, J = 9.5 Hz; 1H), 8.10 (s, 1H, H^{10}), 8.42 (dd, J_1 = 10 Hz, J_2 = 1.5 Hz; 2H), 9.61 (d, J = 9.5 Hz; 1H)	2.31 (4.45), 270 (4.77), 287 (4.69), 323 (4.25), 350 (4.13), 386 (3.87), 401 (3.81), 423 (3.76), 449 (3.64), 493 (3.33), 558 (3.27), 594 (3.52), 661 (2.85), 792 (2.55)
(9a)	1.10 (t, J = 7 Hz; 6H, CH_2—CH_3), 2.34 (s, 3H, CH_3), 2.47 (d, J = 1 Hz; 3H, CH_3), 2.87 (s, 3H, CH_3), 3.05 (q, J = 7 Hz; 4H, CH_2—CH_3), 6.40 (s, 1H), 6.87 (s, 1H), 7.08 (s, 1H), 7.41 (mc, 1H), 7.45 (s, 1H), 7.63 (s, 1H), 7.85 (s, 1H), 8.00 (mc, 1H)	272 (4.52) sh, 300 (4.72) sh, 312 (4.77) sh, 322 (4.80), 352 (4.42) sh, 390 (4.00) sh, 436 (3.91) sh, 454 (4.00), 516 (3.37), 557 (3.19), 647 (2.00) sh, 709 (2.16), 784 (2.21), 880 (2.00) sh, 1042 (1.18) sh
(10)	2.39 (s, 6H, 7-CH_3, 9-CH_3), 3.03 (s, 3H, 2-CH_3), 6.72—6.98 (m, 5H), 7.34 (mc, 2H), 7.98 (s, 2H, H^1, H^3)	231 (3.79), 245 (3.69) sh, 275 (3.87) sh, 285 (3.99) sh, 309 (4.42), 348 (3.33), 367 (3.27), 388 (3.22), 411 (2.46) sh, 426 (2.45), 464 (1.59), 502 (1.78), 621 (2.25), 833 (1.83), 928 (1.81), 1111 (1.41)
(15)	1.81 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 3.45 (mc, 1H, H^{6a}), 3.72 (dd, J_1 = 18.6 Hz, J_2 = 3.7 Hz; 1H, 7-CH_2), 3.99 (dd, J_1 = 18.6 Hz, J_2 = 4.9 Hz; 1H, 7-CH_2), 6.13 (dd, J_1 = 7 Hz, J_2 = 3 Hz; 1H, H^6), 6.42 (dd, J_1 = 7 Hz, J_2 = 1 Hz; 1H, H^5), 7.12 (mc, 2H), 7.56 (s, 1H), 7.64 (s, 1H), 7.78 (mc, 1H), 7.94 (s, 1H)	221 (4.36), 283 (4.84), 356 (3.87), 371 (3.83), 380 (3.68) sh, 461 (3.24), 482 (3.33), 504 (3.23) sh, 650 (2.37) sh, 688 (2.39), 752 (2.29) sh, 860 (1.76) sh

Like *(5b)*, but unlike *(9a)*, the hydrocarbon *(9b)*[6] also reacts with *(6)* in a dipolar cycloaddition at the unsubstituted seven-membered ring. Thereby trimethyldibenzo[4,5;7,8]dicyclopent[*cd,ij*]azulene *(10)* is formed (grayish blue platelets; m.p. 224—225 °C; <10 % yield) in a reaction sequence analogous to the formation of *(7)*. Compound *(10)* is the first fully conjugated thermally stable derivative of the hitherto unknown dicyclopent[*cd,ij*]azulene, which presumably has a high ring strain.

The major product formed besides *(10)*, however, is the ketone *(15)* (greenish yellow needles, m.p. 290 °C; yield 56 %), which is only sparingly soluble in organic solvents. This points to a primary attack of *(6)* on *(9b)* with formation of the resonance-stabilized dipole *(11)*. Subsequent cyclization gives the cyclobutene derivative *(12)*, and valence isomerization of *(12)* *via* the thermally unstable cyclononaazulene derivative *(13)* forms the enamine *(14)*, which yields *(15)* on hydrolysis.

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(1), 67745-88-4; *(2)*, 762-42-5; *(3)*, 67745-89-5; *(4)*, 67745-90-8; *(5b)*, 1213-66-7; *(6)*, 4231-35-0; *(9a)*, 67761-63-1; *(9b)*, 67745-91-9; *(10)*, 67745-92-0; *(15)*, 67745-93-1

[1] a) *K. Hafner, H. Diehl, H. U. Süss*, Angew. Chem. *88*, 121 (1976); Angew. Chem. Int. Ed. Engl. *15*, 104 (1976); *K. Hafner, M. Suda, ibid. 88*, 341 (1976) and *15*, 314 (1976); b) *H. Diehl, K. Hafner, ibid. 88*, 124 (1976) and *15*, 107 (1976); c) *K. Hafner, H. Diehl, W. Richarz, ibid. 88*, 125 (1976) and *15*, 108 (1976).

[2] *H. D. Diesel*, Dissertation, Technische Hochschule Darmstadt 1978.

[3] Correct elemental analyses and mass spectra were obtained for all the compounds described.

[4] *K. Hafner, R. Fleischer, C. Fritz*, Angew. Chem. *77*, 42 (1965); Angew. Chem. Int. Ed. Engl. *4*, 69 (1965).

[5] *R. Zahradník, J. Michl, J. Pancir*, Tetrahedron *22*, 1355 (1966); *B. A. Hess, L. J. Schaad*, J. Org. Chem. *36*, 3418 (1971); *H. J. Lindner*, Tetrahedron *30*, 1127 (1974); *R. Gleiter, M. Böhm*, personal communication.

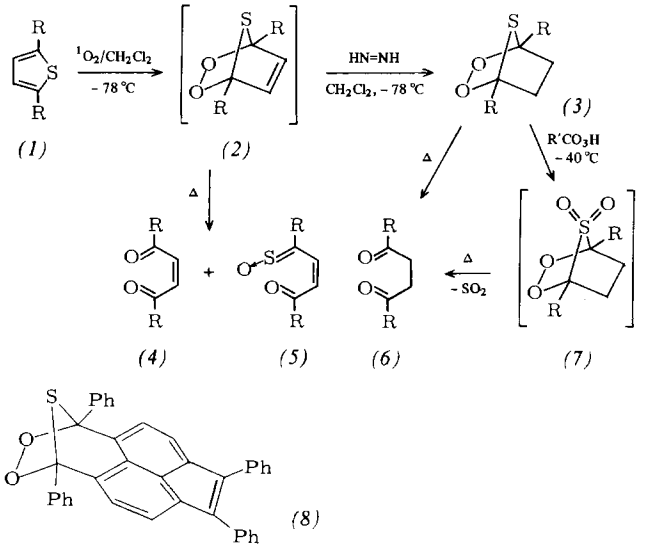
[6] Compound *(9b)* was prepared by analogy with the synthesis of acetheptylene (*K. Hafner*, Pure Appl. Chem. *28*, 153 (1971)) by condensation of the corresponding benzocyclopentazulene [1c] with *N*-methyl-*N*-[3-(*N*-methylanilino)-2-propenylidene]anilinium perchlorate and subsequent thermal cyclization of the initially formed dienamine in boiling quinoline (dark brown needles of m.p. 163 °C; *W. Richarz*, Dissertation, Technische Hochschule Darmstadt 1977).

2,3-Dioxa-7-thiabicyclo[2.2.1]heptane: A New Heterobicyclic System Possessing the Thiaozonide Structure[**]

By *Waldemar Adam* and *Henny J. Eggelte*[*]

To the best of our knowledge thiaozonides possessing the 2,3-dioxa-7-thiabicyclo[2.2.1]heptane structure *(3)* are unknown. The only related substance of this type to have been described[1] is the rather labile and therefore difficult to characterize diphenylacenaphthylene derivative *(8)*.

We now wish to report that thiaozonides *(3a)* and *(3b)* can be prepared in good yields, isolated, and characterized. We have also found that oxidation of electron-rich thiophenes *(1)* with singlet oxygen affords the postulated highly reactive thiophene endoperoxides *(2)*, and that peracid oxidation of the thiaozonides *(3)* leads to 1,4-diones *(6)* by sulfur dioxide elimination, presumably *via* the unusual sulfones *(7)*.



(1) *(2)* *(3)* *(4)* *(5)* *(6)* *(7)*

(8)

(a), R = CH_3; *(b)*, R = $C(CH_3)_3$

Alkyl-substituted thiophenes *(1)* undergo photosensitized reaction with singlet oxygen to afford 2-butene-1,4-dione derivatives *(4)* and sulfenes *(5)*[2], which presumably arise from the labile, intermediary thiophene endoperoxides *(2)* by thermal loss of sulfur or rearrangement, respectively. If the endoperoxides *(2)* really are reaction intermediates in the photooxygenation of thiophenes *(1)*, then it should be possible to reductively trap them with diazene, as recently demonstrated for the unstable endoperoxides of cyclopentadiene[3a], spirocycloheptadiene[3b], fulvene[3c], and α-pyrone[3d].

Indeed, photooxygenation of 2,5-dimethylthiophene *(1a)* in CH_2Cl_2 at −78 °C with tetraphenylporphyrin as sensitizer, followed by diazene reduction of *(2a)*[4] in CH_2Cl_2 at −78 °C[3a], gave a 46% overall yield of thiaozonide *(3a)* after silica gel chromatography at −20 °C and elution with CH_2Cl_2[5]. This compound is thermally unstable and rapidly decomposes at room temperature to 2,5-hexanedione *(6a)*. The same diketone was obtained in essentially quantitative yield by triphenylphosphane desulfurization of *(3a)*[6], confirming the thiaozonide structure *(3)*.

In an analogous manner, 2,5-di-*tert*-butylthiophene *(1b)* was converted into the thiaozonide *(3b)* by diazene reduction of the unstable *(2b)*[4]. Compound *(3b)* was isolated by silica gel column chromatography at −20 °C with CH_2Cl_2 as eluant and could be purified by low temperature recrystallization from pentane. *(3b)* is more stable than *(3a)*, but also decomposes rapidly to 2,2,7,7-tetramethyl-3,6-octanedione *(6b)* at room temperature. The diketone *(6b)* was also obtained in essentially quantitative yield by catalytic hydrogenation over Pd/C, thus confirming the thiaozonide structure *(3)*.

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[1] *J. M. Hoffman, Jr., R. H. Schlessinger*, Tetrahedron Lett. *1970*, 797.
[2] a) *W. J. M. van Tilborg*, Rec. Trav. Chim. Pays-Bas *95*, 140 (1976). b) *C. N. Skold, R. H. Schlessinger*, Tetrahedron Lett. *1970*, 791. c) *H. H. Wasserman, W. Strehlow, ibid. 1970*, 795.
[3] a) *W. Adam, H. J. Eggelte*, J. Org. Chem. *42*, 3987 (1977). b) *W. Adam, I. Erden, ibid. 43*, 2737 (1978). c) *W. Adam, I. Erden*, Angew. Chem. *90*, 210 (1978); Angew. Chem. Int. Ed. Engl. *17*, 223 (1978); d) *ibid. 90*, 211 (1978) and *17*, 223 (1978), resp.
[4] *(2a)*: ^{1}H-NMR ($CFCl_3$, TMS, −21 °C): $\delta = 1.80$ (s, CH_3), 5.78 (s, =CH); decomposes at *ca.* 0 °C.
[5] *(3a)*: yield 46%, viscous oil, which partially decomposed on short path distillation at reduced pressure; ^{1}H-NMR (CCl_4, TMS) $\delta = 1.75$ (s, CH_3, 6H), 2.12 (s, CH_2, 4H); IR (CCl_4) 2980, 2940, 2885, 2855, 1445, 1375, 1300, 1200, 1145, 1120, 1060, 890, 845, 600 cm^{-1}; *(3b)*: yield 50%, white needles, m.p. 68—69 °C (from pentane at −78 °C); ^{1}H-NMR (CCl_4, TMS) $\delta = 1.16$ (s, CH_3, 18H), 2.21 (s, CH_2, 4H); IR (CCl_4) 2970, 2905, 2870, 1460, 1395, 1365, 1185, 1105, 1080, 1040, 900, 630 cm^{-1}.
[6] *J. Carles, S. Fliszar*, Can. J. Chem. *47*, 1113 (1969).

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[**] Cyclic Peroxides, Part 69. Acknowledgements are made to the Donors of the Petroleum Research Fund (Grant 8341-AC-1,4), administered by the American Chemical Society, the National Science Foundation (Grant CHE-77-13308), and the National Institutes of Health (Grants GM-21119-03, GM-00141-02 and RR-8102-03). Part 68: *W. Adam, K. Sakanishi*, J. Am. Chem. Soc. *100*, 3965 (1978).

Synthesis and Stereochemical Consequences of Protonation of a Bishomodihydrotetraaza[14]annulene: A New Macrocyclic Complex Ligand[**]

By *Helmut Quast, Josef Stawitz, Karl Peters*, and *Hans Georg von Schnering*[*]

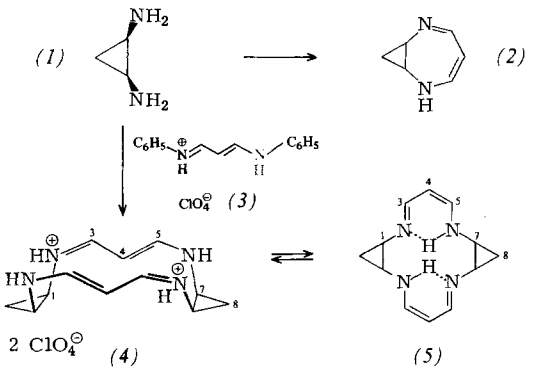
Unsaturated fourteen-membered heterocycles having two[1] or four[2] nitrogen atoms are sometimes formed with surprising ease instead of azepines or diazepines despite the absence of transition metal ions acting as template. Derivatives of tetraaza[14]annulenes are of interest because of their ability to complex transition metal ions[3]. On preparation of the diazahomotropilidene *(2)* from *cis*-1,2-cyclopropanediamine *(1)*[4] we observed the formation of bishomodihydrotetraaza[14]annulene *(5)*. This compound exhibits a drastic change of structure on protonation hitherto known only for corresponding acyclic compounds such as the base underlying the perchlorate *(3)*[5]. Moreover, *(5)* also warrants attention as

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a new complex ligand and, because of its periphery of 16 atoms, as a potential precursor of porphinoid systems[6].



Reaction of the dihydrochloride of *(1)*, malondialdehyde dianil perchlorate *(3)*, and sodium acetate in methanol gives a product whose hot aqueous solution precipitates a colorless diperchlorate *(4)* on addition of sodium perchlorate. Treatment of *(4)* with sodium methoxide in methanol gives the base *(5)* as pale yellow needles of m.p. 147—149°C, which exhibit recrystallization at *ca.* 155°C (without any change in the IR spectrum) and a second m.p. at 185°C.

The gross structure of the diperchlorate *(4)* and the free base *(5)* follows from elemental analysis, IR[7], and ^{1}H-NMR spectra (Table 1), and from the mass spectrum of *(5)*. The broadened NH band of *(5)* is independent of concentration. This finding and the downfield shift of the *N*-protons[2c, 5] suggest intramolecular hydrogen bonding.

The ^{1}H-NMR spectra of *(4)* and *(5)* each contain just *one* ABX_2 spectrum for the cyclopropane protons and just *one* AX_2 spectrum for the methine protons, and thus assign a symmetry to the two compounds that may (as always) also be due to fast dynamic processes. The small coupling constants of the methine protons of *(5)* prove the cisoid configuration of the N2—C3—C4—C5—N6 and N10—C11—C12—C13—N14 units[5] expected from intramolecular hydrogen bonds. On the other hand, the methine protons of *(4)* exhibit almost the same coupling constant as in *(3)*[5] and other *trans*-configurated trimethine cyanines[8]. While this confirms the transoid configuration of the corresponding systems in *(4)* no further information is available from the NMR spectrum about the other bonds of the fourteen-membered ring or about the relative arrangement of the cyclopropane rings.

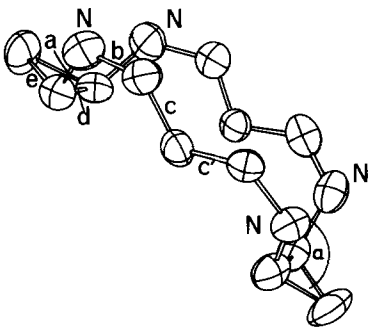
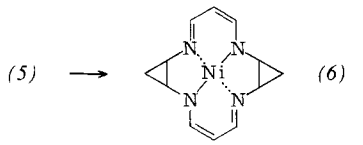


Fig. 1. Structure of the diperchlorate *(4)*. The compound forms monoclinic crystals of space group $P2_1/n$ (No. 14); $a = 1154.2$, $b = 1716.9$, $c = 915.1$ pm, $\beta = 101.19°$, $Z = 4$; Syntex $P\bar{1}$ four-circle diffractometer; scintillation counter; MoKα radiation; $2\theta \leq 55°$; 2642 *hkl* with $I > 2\sigma(I)$; $R_{aniso} = 0.084$ (H atoms isotropic); site disorder in one of the $ClO_4^\ominus$ ions. Average bond lengths: $a = 143.1$, $b = 131.9$, $c = 137.9$, $d = 151.7$, and $e = 149.2$ pm. The individual distances deviate from the average values by at most 5 pm. Bond angles and torsional angles: $a/b = 123.7$, $b/c = 124.6$, $c/c' = 118.6$, $a/d = 120.1$, $a/e = 117.5°$; $a/b/c = 1.0$ and $b/c/c' = 8.6°$.

charge delocalization. The three-membered rings are inclined to the plane formed by the neighboring bonds *a* by $\alpha = 106.1°$.

Brief heating of *(5)* with nickel(II) acetate tetrahydrate in ethanol to 70°C affords a nickel complex as a green powder that is readily soluble in nonpolar solvents such as toluene; its mass spectrum ($m/e = 272$, 100%, M^+) and ^{1}H-NMR spectrum (Table 1) indicate structure *(6)*. Solutions of *(6)* are air-sensitive and on standing they deposit an insoluble bluish-black substance which is presumably polymeric[2a].



Procedure

(1)·2HCl (1.45 g, 10 mmol), sodium acetate (1.66 g, 20 mmol), and *(3)* (3.22 g, 10 mmol) were stirred together in methanol (500 ml) at 25°C for 3 d. The residue obtained on evaporation in vacuum was digested with ether (200 ml) and washed with ethanol (12 ml). Compound *(4)* was obtained as colorless crystals (m.p. 309—312°C; yield 676 mg, 32%) from aqueous solution (charcoal) by addition of sodium perchlorate.

Table 1. ^{1}H-NMR data (90 MHz) of the diperchlorate *(4)* in [D]trifluoroacetic acid and of the base *(5)* and the nickel complex *(6)* in [D]chloroform. Only one set of equivalent protons is listed. The values of the ABX_2 spectrum of the cyclopropane protons were optimized with the aid of the LAOCOON III computer program.

Cpd.	2-H	Methine protons 3-H (d)	4-H [a] (t)	$J_{3,4}$	7-H	Cyclopropane protons 8-H (*endo*)	8'-H (*exo*)	$J_{7,8}$ (*trans*)	$J_{7,8'}$ (*cis*)	$J_{8,8'}$
(4) [b]	7.9 [c]	7.84	6.41	12.4	3.38	1.67	2.01	5.57	8.63	−8.55
(5)	9.88	7.38 [d]	4.62	5.86	2.88	0.68	1.14	4.48	7.54	−6.12
(6)	—	7.01	4.76	6.00	3.05	0.50	0.86	3.46	7.18	−5.78

[a] Replaced by D in [D]trifluoroacetic acid after addition of $[D_2]$sulfuric acid or in [D]methanol in the presence of sodium methoxide (at 40°C).
[b] ABX_2 spectrum at 106°C; at 30°C the AB part is slightly broadened.
[c] In trifluoroacetic acid $J_{2,3} = 7$ Hz. [d] Exhibits signal broadening which disappears on shaking with D_2O.

X-Ray structure analysis of the diperchlorate *(4)* (Fig. 1) revealed the structural details of the cyclic dication; it has C_{2v} symmetry within the standard deviations. The bonds *b*, *c*, *c*, *b'* form two separate "open" 6π systems with extensive

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(1) di-HCl, 63466-89-7; *(3)*, 2581-81-5; *(4)*, 67761-28-8; *(5)*, 67814-41-9; *(6)*, 67761-37-9

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[6] *J. Löliger, R. Scheffold*, Helv. Chim. Acta *60*, 2644 (1977).

[7] IR: *(4)* (KBr): $\tilde{\nu}$ = 3150 (NH), 1645, 1630, 1535 cm^{-1} (C=N, C=C); *(5)* (CCl_4): $\tilde{\nu}$ = 3140 (NH), 1635, 1570 cm^{-1} (C=N, C=C).

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Decamethyl-1λ³,4λ³-diphospha-2,3,5,6,7-pentastannabicyclo[2.2.1]heptane, a Bicyclic Compound Rich in Tin[**]

By *Bernd Mathiasch* and *Martin Dräger*[*]

Dimethylstannane *(1)* reacts with chalcogens to give chalcogen hydrides and compounds containing tin-chalcogen bonds; in the presence of catalytically active bases, hydrogen and compounds containing tin-tin bonds are formed (cf. [1]).

We have now found that base-catalyzed reaction of *(1)* with white phosphorus affords hydrogen, phosphane, and 2,2,3,3,5,5,6,6,7,7-decamethyl-1λ³,4λ³-diphospha-2,3,5,6,7-pentastannabicyclo[2.2.1]heptane (pentakis(dimethyltin) diphosphide) *(2)* in 62% yield:

$$5(CH_3)_2SnH_2 + P_4 \xrightarrow[Et_2O/295\,K]{DMF} 2H_2 + 2PH_3 + [(CH_3)_2Sn]_5P_2$$
(1) *(2)*

In the absence of organic bases (dimethylformamide, pyridine) mainly the already well-known hexakis(dimethyltin) tetraphosphide *(3)* is formed[2]:

$$6(CH_3)_2SnH_2 + 2P_4 \xrightarrow[Et_2O/295\,K]{} 4PH_3 + [(CH_3)_2Sn]_6P_4$$
(1) *(3)*

Organotin hydrides containing tin-tin bonds react under these conditions to give heterocycles still more rich in tin; *e.g.* tetramethyldistannane *(3)* reacts with white phosphorus to give hexakis(dimethyltin) diphosphide *(5)*[3]:

$$3(CH_3)_4Sn_2H_2 + P_4 \xrightarrow[Et_2O/273\,K]{} 2PH_3 + [(CH_3)_2Sn]_6P_2$$
(4) *(5)*

On recrystallization from benzene, *(2)* forms colorless, strongly refracting crystals which decompose only slowly at room temperature, but rapidly with discoloration at temperatures above 400 K. An X-ray structure[4] of *(2)* showed the molecule to have ideal C_{2v} symmetry with measured bond lengths within 2σ (Fig. 1).

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

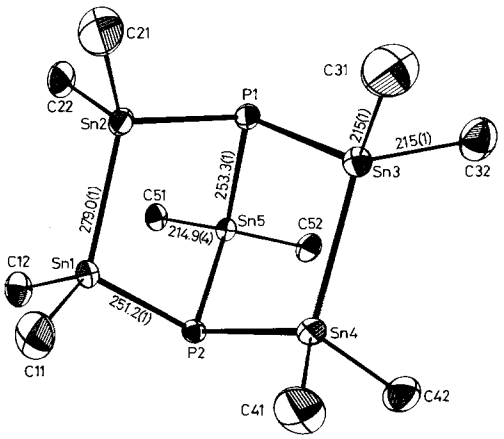


Fig. 1. Molecular structure of *(2)*, with bond lengths in pm. The torsion angles about the tin-tin bonds, like the corresponding angles in norbornane [5] are 0°. Representative bond angles and torsion angles [°]:

Sn1—Sn2—P1	106.8(1)	P2—Sn1—Sn2—P1	0.1(3)
Sn2—P1—Sn3	102.2(1)	Sn1—Sn2—P1—Sn3	68.1(1)
Sn2—P1—Sn5	93.7(1)	Sn1—Sn2—P1—Sn5	26.5(1)
P1—Sn5—P2	113.6(1)	Sn2—P1—Sn5—P2	51.2(1)
C11—Sn1—C12	107.3(2)		
C51—Sn5—C52	111.7(2)		

As shown by the ^1H- and ^{13}C-NMR spectra, the rigid bicyclic skeletal structure of *(2)* is retained in solution. Three types of methyl groups can be distinguished, both by their chemical shift[6] as well as by their couplings to ^{31}P and $^{117/119}Sn$.

The extent of the ^3J(PSnCH) and the ^2J(PSnC) coupling is strongly dependent upon the position of the coupling groups (nuclei) in relation to the non-bonding orbital on the phosphorus atom (Table 1), whose direction was determined by two methods[7].

Table 1. Torsion angles/coupling constants [7] (cf. text).

Torsion angle	[°]	41	61	76
^2J(PSnC)	[Hz]	10.3	8.4	5.9
^3J(PSnCH)	[Hz]	3.3	2.1	1.5
$^2J(^{119}$SnCH)	[Hz]	49.7	45.4	47.4
$^1J(^{119}$SnC)	[Hz]	205		200

Experimental

A mixture of *(1)* (3.6 g, 24 mmol) in 50 ml ether/0.5 ml dimethylformamide and 0.6 g (19 mmol) of white phosphorus is gently stirred for 12 h at room temperature in an Ar-filled flask furnished with a rubber balloon. Dissolution of the phosphorus is accompanied by precipitation of needle-shaped colorless crystals. The reaction mixture is allowed to warm to *ca.* 300 K, filtered under argon, and the residue recrystallized from dichloromethane. On cooling to 240 K the filtrate yields a further fraction of *(2)*; total yield 2.4 g (62%).

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CAS Registry numbers:
(1), 2067-76-7; *(2)*, 67761-26-6; P_4, 12185-10-3

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[3] *B. Mathiasch*, unpublished.

[4] Cell data: a = 824.9(2), b = 1003.1(2), c = 1456.2(2) pm, α = 80.09(3), β = 82.53(4), γ = 86.22(5)°, $V = 1.176 \times 10^9$ pm^3, space group $P\bar{1}$, Z = 2, $\rho_{X\text{-ray}}$ = 2.28, ρ_{exp} = 2.28 $g\,cm^{-3}$, 5392 reflections (λ = 71.069 pm), 644 less than $<2\sigma$, CAD4 diffractometer, R = 0.0259, R_w = 0.0308. H atoms not considered.

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[6] $\delta(^1H)=0.39$ (t, C51, C52), 0.42 (d, C12, C22, C32, C42), and 0.46 (d, C11, C21, C31, C41); $\delta(^{13}C)=-2.1$ (t), -4.7 (d), and -5.1 (d); both spectra rel. TMS, CD_2Cl_2-soln., 2.114 T.

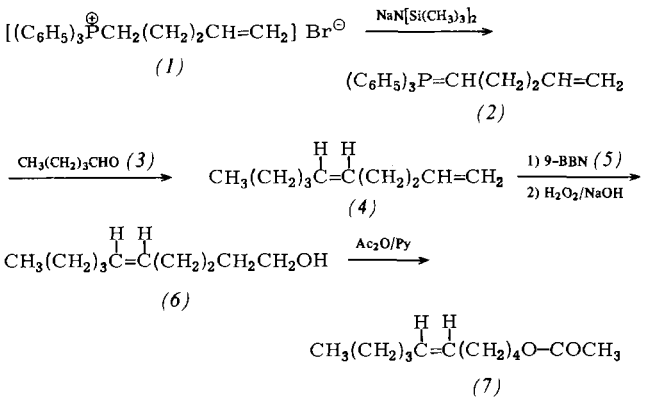
[7] Method 1: tetrahedral extension on phosphorus atom; method 2: connecting line between the mass center of the triangle (Sn2Sn5Sn3) and P1; both methods afford the same numerical results.

(*Z*)-5-Decenyl Acetate, a Sex Attractant for the Male Turnip Moth *Agrotis segetum* (Lepidoptera)[**]

By *Hans Jürgen Bestmann, Otto Vostrowsky, Karl-Heinz Koschatzky, Hans Platz, Thorolf Brosche, Iwan Kantardjiew, Marlies Rheinwald*, and *Werner Knauf*[*]

The turnip moth *Agrotis* (=*Scotia*) *segetum* (Noctuidae, Lepidoptera) is an ubiquitous grain pest, which up to the present time has proved very difficult to control. An electroantennogram screening (EAG screening)[1,2] with *ca.* 100 unsaturated aldehydes, alcohols, and their acetates on the antennas of the male species of the insects showed that (*Z*)-5-decenyl acetate *(7)* caused the greatest excitation. We still found EAG responses on loading the stimulus source with as little as 10^{-5} µg of *(7)*. As expected[2,3] (*Z*)-7-dodecenyl acetate also exhibits high EAG activity.

We have synthesized *(7)* according to Scheme 1.



Scheme 1.

The phosphonium salt *(1)*, obtainable from 4-pentenyl bromide and triphenylphosphane, is converted by the silazide method[4] into the ylide *(2)*, which reacts with pentanal *(3)* at -78 °C in a (*Z*)-stereoselective Wittig reaction to give 1,(*Z*)-5-decadiene *(4)*, b.p. 55—57 °C/14 torr, yield 62%. Hydroboration of *(4)* with 9-borabicyclo[3.3.1]nonane *(5)* (9-BBN) and subsequent oxidation with H_2O_2 affords the alcohol *(6)*, b.p. 114—115 °C/14 torr, yield 82%, which on acetylation gives the acetate *(7)*, b.p. 105—107 °C/16 torr, yield 87%.

In order to identify the natural pheromone the abdominal tips with sex glands were excised from 500 females and together extracted with hexane. The pheromone extract was filtered and separated chromatographically on a silica gel column (0.06—0.2 mm, 30 × 1.5 cm) with an eluent system of increasing polarity (pentane/diethyl ether/methanol) into 17 fractions, the physiological activity of which was determined by means of the EAG test. The active fractions were combined, concentrated in a stream of nitrogen and analyzed by capillary gas chromatography synchronously with a flame ionization detector and EAG detector[5]. The EAG detector showed a physiologically active compound having the retention time of (*Z*)-5-decenyl acetate *(7)*. Cochromatography of synthetic *(7)* gave retention times identical with those of the contents of the gland substances.

Proof of the presence of *(7)* in the sex glands of the females was provided by an analysis of the extract by coupled capillary gas chromatography—mass spectroscopy. 17 ions[6] were inferred from the mass spectrum of synthetic *(7)*. All these ions could be determined simultaneously in the chromatogram of the extract, precisely at the previously determined retention time of *(7)*. For further proof of the structure, the pheromone extract was separated gas chromatographically on a packed column; fractions were collected at minute intervals in cooled glass capillaries. Once again, according to the EAG test the activity was found in the fraction having the retention time of synthetic *(7)*.

Synthetic (*Z*)-5-decenyl acetate *(7)* was transferred to a multistep single-tube olfactometer[7], monitored with an automatic television camera fitted with time scanning and magnetic tape printout, and its efficacy as an attractant for male turnip moths was checked. *(7)* proved to have a luring effect up to attractant loadings of 10^{-6} µg, whereas above 10^{-3} µg an inhibiting effect was observed.

Trapping of the male species in open wind-socks was still recorded at a loading of 5×10^{-4} µg of *(7)*; more than 0.5 µg of *(7)* has an inhibiting effect.

Thus, (*Z*)-5-decenyl acetate *(7)* has been identified for the first time as a sex attractant for Lepidoptera. It is more effective than any of the previously reported butterfly pheromone components.

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CAS Registry numbers:
(1), 56771-29-0; *(2)*, 67773-68-6; *(3)*, 110-62-3; *(4)*, 67773-69-7; *(5)*, 280-64-8; *(6)*, 51652-47-2; *(7)*, 67446-07-5

[1] *D. Schneider*, Z. Vgl. Physiol. *40*, 8 (1957).
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[4] *H. J. Bestmann, W. Stransky, O. Vostrowsky*, Chem. Ber. *109*, 1694 (1976).
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[6] *m/e* = 138 ($C_{10}H_{18}$), 137 ($C_{10}H_{17}$), 110 (C_8H_{14}), 109 (C_8H_{13}), 96 (C_7H_{12}), 95 (C_7H_{11}), 94 (C_7H_{10}), 93 (C_7H_9), 81 (C_6H_9), 80 (C_6H_8), 79 (C_6H_7), 73 (CH_2OCOCH_3), 67 (C_5H_7), 66 (C_5H_6), 65 (C_5H_5), 61 (CH_3COOH_2), and 60 (CH_3COOH); Finnigan 3200 E with Finnigan 6000 data system. The mass spectrum of the sex attractant could not be recorded since the content in the extract was extremely low. We estimate that only *ca.* 0.1 ng was extracted from each female.
[7] *W. Knauf, O. Vostrowsky, H. J. Bestmann*, unpublished.

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[**] Pheromones, Part 22.—Parts 20 and 21: *H. J. Bestmann, J. Süss, O. Vostrowsky*, Tetrahedron Lett. *1978*, in press.

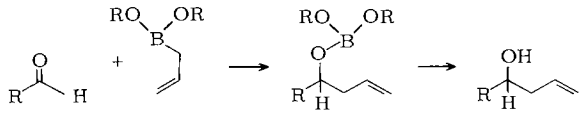
Enantioselective Synthesis of Homoallyl Alcohols *via* Chiral Allylboronic Esters

By *Thomas Herold* and *Reinhard W. Hoffmann*[*]

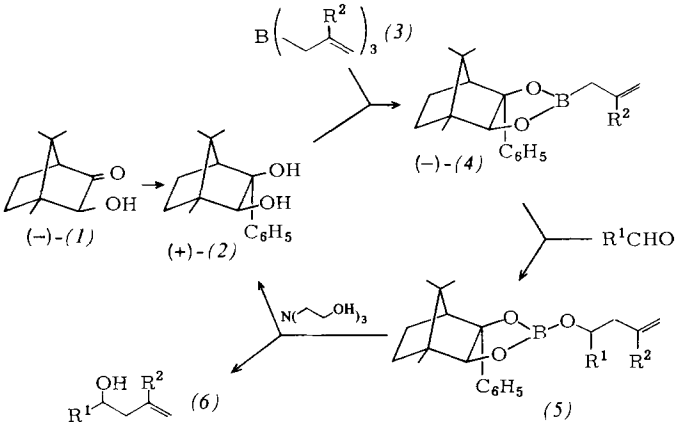
We report on the enantioselective synthesis of secondary homoallyl alcohols of type *(6)* by a modification of the

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known[1] addition of allylboronic esters to aldehydes. This procedure improves upon and supplements existing methods[2] for the enantioselective conversion of aldehydes into secondary alcohols.



We used the glycol *(2)* [obtained from (+)-camphor *via* the ketol *(1)*[3] and its reaction with phenyllithium in ether] as chiral matrix. Reaction of equimolar amounts of the allylboranes *(3)*[1] and *(2)* (THF, 30 min, 50 °C) yielded more than 95 % of the allylboronic esters (−)-*(4)* after vacuum distillation. A 2 M solution of *(4)* reacted (*n*-hexane, 1 h at −40 °C, 12 h at 25 °C) with an equivalent amount of an aldehyde to give the borates *(5)*, from which the alcohols *(6)* were obtained directly by cleavage with 1.2 equiv. of triethanolamine (2 h, 25 °C) (Table 1).



Except in the case of *(6f)*, the alcohols *(6)* were purified by vacuum distillation; the chiral glycol (+)-*(2)* was recovered in approximately 80 % yield by chromatography on silica gel with CH_2Cl_2. The whole sequence *(2)* → *(6)* can also be effected in a one-pot process without isolation of intermediates.

Table 1. Enantiomeric excesses and yields in the synthesis of the alcohols *(6)*.

	R^1	R^2	$[\alpha]_D^{20}$	*c* solv. [a]	e.e. [%] [b]	Yield [%] [c]
(6a)	Me	H	− 6.35	9.13 E	65 (*R*)	92
(6b)	Et	H	+ 4.74	10.76 B	77 (*R*)	91
(6c)	*n*-Pr	H	+10.37	10.22 B	72 (*R*)	93
(6d)	*i*-Pr	H	− 2.62	11.82 B	70 (*S*)	88
(6e)	*t*-Bu	H	− 5.32	10.90 B	45 (*S*)	85
(6f)	$(CH_3)_2CCl$	H	−22.16	9.43 D	70 (*S*)	83
(6g)	Me	Me	− 5.15	8.35 E	74 (*R*)	82
(6h)	Et	Me	+ 5.13	3.51 E	70 (*R*)	85
(6i)	*n*-Pr	Me	+23.08	2.60 E	65 (*R*)	84
(6j)	*i*-Pr	Me	− 1.40	8.46 E	76 (*S*)	87
(6k)	*t*-Bu	Me	− 3.10	8.39 E	70 (*S*)	92

[a] Solvents: E = diethyl ether, B = benzene, D = dichloromethane. [b] The enantiomeric excess of the alcohols *(6)* was determined in most cases by ^{19}F-NMR spectroscopy according to *Mosher* [4]. [c] Isolated yields of *(6)* based on (−)-*(4)*.

The enantiomeric excesses are surprisingly constant for various aldehydes with a (sp^3-C)—CHO structure. With benzaldehyde, however, and other aldehydes with a (sp^2-C)—CHO structure the values range from 24 to 54 %.

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CAS Registry numbers:
(−)-*(1)*, 23963-16-8; (+)-*(2)*, 67814-35-1; *(3a)*, 688-61-9; *(3g)*, 32784-73-9; (−)-*(4a)*, 67760-74-1; (−)-*(4b)*, 67760-75-2; *(5a)*, 67760-76-3; *(5b)*, 67760-77-4; *(5c)*, 67760-78-5; *(5d)*, 67784-50-3; *(5e)*, 67784-49-0; *(5f)*, 67760-79-6; *(5g)*, 67760-80-9; *(5h)*, 67760-81-0; *(5i)*, 67760-82-1; *(5j)*, 67760-83-2; *(5k)*, 67784-53-6; *(6a)*, 64584-92-5; *(6b)*, 62959-96-0; *(6c)*, 67760-84-3; *(6d)*, 67760-85-4; *(6e)*, 67760-86-5; *(6f)*, 67760-87-6; *(6g)*, 67760-88-7; *(6h)*, 67760-89-8; *(6i)*, 67760-90-1; *(6j)*, 67760-91-2; *(6k)*, 67760-92-3; acetaldehyde, 75-07-0; propanal, 123-38-6; butanal, 123-72-8; 2-methylpropanal, 78-84-2; 2,2-dimethylpropanal, 630-19-3; 2-chloro-2-methylpropanal, 917-93-1

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Functional Derivatives of D- and L-Ribose by Optical Resolution with Recycling[**]

By *Richard R. Schmidt* and *Albrecht Lieberknecht*[*]

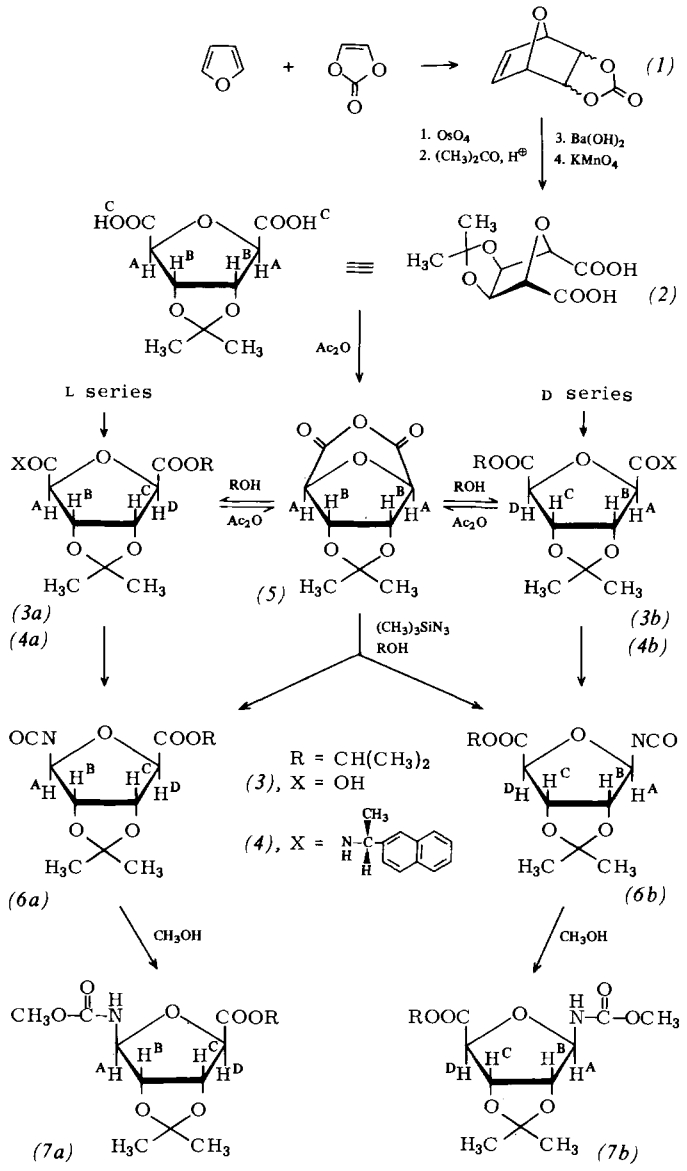
Starting from furan and the readily accessible vinylene carbonate[1] we have developed a chirally economic synthesis[2] of the functional D- and L-riburonic acid derivatives *(6a)* and *(6b)*[3]. These compounds are valuable intermediates for the synthesis of biologically important nucleosides and nucleoside uronic acids[4] and sugar-amino acid conjugates[5].

Five straightforward reaction steps without isolation of intermediates transform the *meso*-Diels-Alder adduct *(1)*[1] (mixture of diastereomers) into the cyclic *meso*-anhydride *(5)* (purified by distillation) in 40 % overall yield (Table 1). Compound *(1)* is specifically transformed by osmium tetroxide into the *exo,exo*-dihydroxy derivative, which is subsequently isopropylidenated at the hydroxy groups; removal of the carbonate protecting group by barium hydroxide and oxidation by potassium permanganate converts the mixture of diastereomers into the sterically uniform *meso*-1,5-anhydroallaric acid *(2)* which contains the principal configurational components of D- and L-ribose[6]; reaction with acetic anhydride gives the *meso*-anhydride *(5)*, which assumes a key role in the further synthesis.

Reaction of *(5)* with trimethylsilyl azide quantitatively yields a racemate of the ribofuranosyl isocyanates *(6a)* and *(6b)*. This reaction removes the *meso* structure of *(5)* and irreversibly generates a mixture of enantiomers which reacts with methanol to give the enantiomeric urethanes *(7a)* and *(7b)*.

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[**] *De-novo* Synthesis of Sugars, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 1: *R. R. Schmidt, R. Angerbauer*, Angew. Chem. *89*, 822 (1977); Angew. Chem. Int. Ed. Engl. *17*, 783 (1977).



A chirally economic synthesis is characterized by recycling of the undesired isomer. To this end the *meso* structure of *(5)* must be reversibly effaced. This is accomplished by alcoholysis with isopropanol. The enantiomeric dicarboxylic monoesters *(3a)* and *(3b)* fulfill all the requirements of this concept for directed asymmetric synthesis (Table 1):

- Optical resolution of *(3a)* and *(3b)* is possible with brucine. The course of resolution was monitored chromatographically by means of the diastereomeric (*R*)-1-(β-naphthyl)-ethylamides *(4a)* and *(4b)*[8] which also permit assignment of configuration[7]. No racemization was observed under the conditions of resolution and isolation of the monoester *(3a, b)*.
- After prior activation of the carboxyl group of *(3b)* with chloroformic ester, β-D-ribofuranosyl isocyanate *(6b)* can be produced stereospecifically *in situ* from *(3b)* with trimethylsilyl azide[9].
- The *meso*-anhydride *(5)* is conveniently regenerated from the monoester *(3a, b)* with acetic anhydride.

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CAS Registry numbers:
(1), isomer A, 32384-16-0; *(1)*, isomer B, 32384-17-1; *(2)*, isomer A, 67761-41-5; *(2)*, isomer B, 67814-44-2; *rac-(3)*, 67761-42-6; *(3a)*, 67814-45-3; *(3b)*, 67814-46-4; *(4a)*, 67761-43-7; *(4b)*, 67814-47-5; *(5)*, 67761-44-8; *rac-(6)*, 67761-45-9; *(6b)*, 67784-52-5; *rac-(7)*, 67761-46-0

[1] *M. S. Newman, R. W. Addor*, J. Am. Chem. Soc. *77*, 3789 (1959); *88*, 3885 (1966).
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[3] *A. Lieberknecht*, Diplomarbeit and Dissertation, Universität Stuttgart 1975 and 1978, respectively.
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[5] *R. D. Marshall, A. Neuberger:* Methods in Carbohydrate Chemistry. Academic Press, New York 1976, Vol. VII, p. 212, references cited therein.
[6] *(2)* and *(3)* are also suitable for the synthesis of *C*-nucleosides. Intermediates for the synthesis of *C*-nucleosides were also obtained from other non-carbohydrate reactants: *R. Noyori, T. Sato, Y. Hayakawa*, J. Am. Chem. Soc. *100*, 2561 (1978), references cited therein, especially [2a]; *A. P. Kozikowski, W. C. Floyd*, Tetrahedron Lett. *1978*, 19.
[7] *G. Helmchen, H. Völter, W. Schühle*, Tetrahedron Lett. *1977*, 1417.—We are grateful to Dr. *G. Helmchen* for his help in the use of this method.
[8] Production of *(4a)* and *(4b)*: conversion of *(3a)* and *(3b)* by ethyl chloroformate into the mixed anhydride, which is reacted with (*R*)-1-(β-naphthyl)ethylamine.
[9] *R. R. Schmidt, D. Heermann, K. H. Jung*, Justus Liebigs Ann. Chem. *1974*, 1856.

Table 1. Compounds prepared [a].

Cpd.	Yield [%]	M.p. [°C] B.p. [°C/torr]	^{1}H-NMR (δ values, $CDCl_3$, TMS int.) H^A	H^B	H^C	H^D
(2)	57 [b]	>300	5.10 (s)	4.55 (s)	11.60 (s)	—
(3a, b) [c]	quant.	70—72	5.1 . . .	4.7 (m)		
(4a) [d]	58	oil	5.4 . . .	4.8 (m)		
(4b) [d]		oil	5.4 . . .	4.7 (m)		
(5)	70 [e]	135 170—180/10^{-3} [f]	5.00 (s)	4.93 (s)	—	—
(6a, b) [g]	quant. [h]	160—170/10^{-3} [f]	5.10 (s)	4.73 (d)	4.89 (dd)	4.63 (d)
(7a, b)	84	oil	5.66 (d)	4.73 (d)	4.90 (dd)	4.62 (d)

[a] All compounds gave correct elemental analyses. [b] Overall yield of *(1)*. [c] Single fractional crystallization of the brucine salts from ethyl acetate/light petroleum (low boiling) gives *(3b)* in 71% enantiomeric excess. [d] *(4a)* and *(4b)* were separated by chromatography (silica gel, light petroleum/ethyl acetate = 7:3); $R_f = 0.40$; *(4a)* (L series). $R_f = 0.48$: *(4b)* (D series) [7]. [e] From *(3a, b)* with acetic anhydride, 87% *(5)*. [f] Oven temperature on bulb-to-bulb distillation. [g] $\tilde{\nu}_{NCO}$ (KBr) = 2150 cm^{-1}. [h] From *(3b) via* the mixed anhydride with ethyl chloroformate 76% *(6b)*; [c].

Synthesis of the Tetrasaccharide Chains of the Determinants of Blood Group Substances A and B[**]

By *Hans Paulsen* and *Čeněk Kolář*[*]

The terminal carbohydrate chain of blood group substances of the AB0 system represent the determinant structure of the antigen responsible for the high immunological specificity of these glycoproteins[1]. After having developed a new stereoselective method for the preparation of α-glycosidically linked 2-amino-2-deoxy-D-galactose[2], we have now succeeded in synthesizing the terminal carbohydrate chains of the blood group substances A, B, and H.

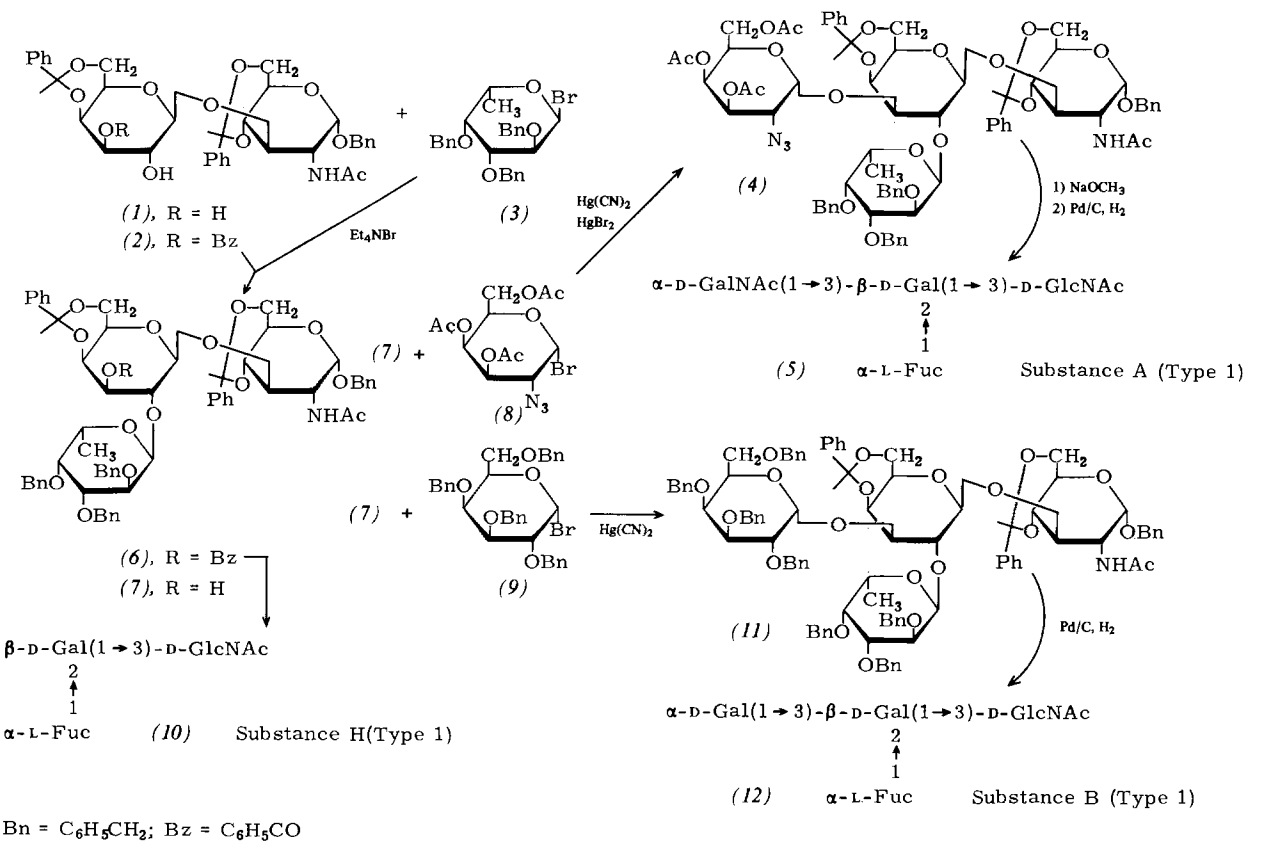
As starting substance we used the readily accessible disaccharide benzyl-2-acetamido-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[3], which after selective cleavage of the *O*-acetyl groups and subsequent reaction with benzaldehyde affords the bis-(benzylidene) compound *(1)*. *(1)* can be selectively benzoylated at the OH group on C-3 to give *(2)*[4]. The fucose residue can then be linked to the remaining 2'-OH group of *(2)* by reaction with the bromide *(3)* to give *(6)* in 82% yield. On halide ion catalysis this reaction affords only the α-L product[5]. The 3'-OH group can be released again by selective alkaline hydrolysis with formation of *(7)*. Complete deblocking by hydrogenation affords the chain *(10)* of the H substance (Type 1)[5] ($[\alpha]_D^{20} = -15.4°$) in 74% yield based on *(7)*.

The trisaccharide *(7)* can react directly with the α-bromide *(8)*, and, in the presence of $Hg(CN)_2/HgBr_2$, yields the α-D-linked tetrasaccharide *(4)* in 63% yield. The inversion technique generally used by us[2,6] [conversion of *(8)* into the β-chloride and subsequent transformation into the α-glycoside] is unnecessary in this reaction. The tetrasaccharide chain *(5)* of the blood group substance A (Type 1) ($[\alpha]_D^{20} = 53.8°$) can be obtained in 77% yield (based on *(4)*) from *(4)* by deblocking with sodium methoxide and hydrogenolytic cleavage.

The blood group substance B can be obtained in the same way from the trisaccharide *(7)*. The galactosyl bromide *(9)* reacts with *(7)* in the presence of $Hg(CN)_2$[7] also to give the α-D-linked tetrasaccharide *(11)* (in 73% yield). The tetrasaccharide chain *(12)* of the blood group substance B (type 1) ($[\alpha]_D^{20} = 33.3°$) is obtainable from *(11)* in a deblocking step by hydrogenolytic cleavage with Pd/C in glacial acetic acid (yield 82% based on *(11)*).

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German version: Angew. Chem. *90*, 823 (1978)

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Bn = $C_6H_5CH_2$; Bz = C_6H_5CO

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[**] Building Units of Oligosaccharides, Part 14. – Part 13: *H. Paulsen, O. Lockhoff, B. Schröder, W. Stenzel*, Carbohydr. Res., in press.

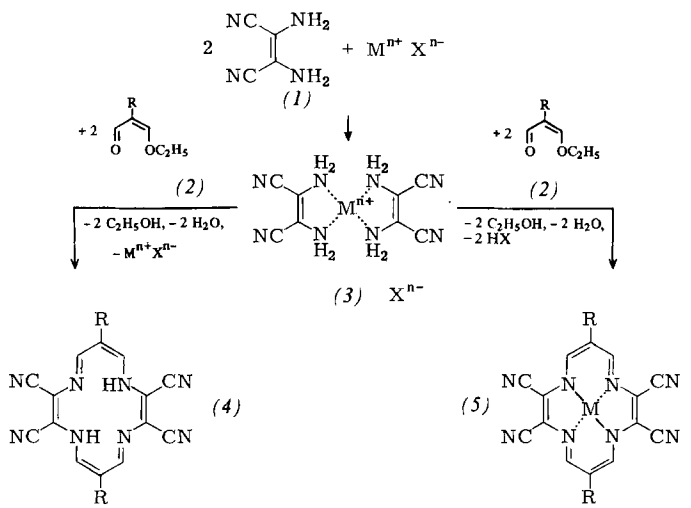
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Direct Synthesis of Metal-Free 1,8-Dihydrotetraaza-[14]annulenes Utilizing the Metal-Template Effect[**]

By *Gerhold Mühmel* and *Eberhard Breitmaier*[*]

Metal chelates of type *(5)*, M = Ni, are formed by cyclocondensation of enediamines *(1)* and 3-ethoxyacroleins *(2)* in the presence of nickel(II) ions[1]. This synthesis, giving yields of about 90 %, is facilitated by the favorable arrangement of two enediamine groups in complex *(3)* and by the stability of the resulting macrocyclic metal chelate (metal-template effect[2]). However, the metal-free macroheterocycle *(4)* is often preparable in only poor yield from *(5)*.

During our experiments concerned with the preparation of metal chelates 6,13-dialkyl-1,8-dihydro-1,4,8,11-tetraaza[14]-annulene-2,3,9,10-tetracarbonitriles by the reaction sequence *(1)* → *(3)* → *(5)* we found that the metal-free macroheterocycles *(4)* are formed directly if the metal ion M^{n+} has an ionic radius[3] significantly smaller or larger than 70 pm. Thus we obtained complexes of type *(5)* with Ni^{2+} (r = 69 pm), Co^{2+}, Cu^{2+} (both with r = 72 pm), Fe^{2+}, and Zn^{2+} (both with r = 74 pm). On the other hand, Mg^{2+} having r = 66 pm and Mn^{2+} having r = 80 pm already afford the macroheterocycle *(4)*. In view of the expected selectivity of the ligands *(4)* this finding initially appears trivial. It is however of preparative significance that the yields of *(4)* obtained by the



sequence *(1)* → *(3)* → *(4)* in a one-pot reaction in the presence of certain metal ions are considerably higher than when the same reaction is conducted without metal ions (see Table 1). Of decisive importance for the effective synthesis of *(4)* is the low selectivity of this ligand for the (oversize or undersize) metal ion. To our knowledge this variant of metal-template synthesis has not been employed previously.

Table 1. Template effect of metal ions on the yield of *(4)*. Reactions performed in ethanol.

MX	r (M^{n+}) [pm]	R	t [h]	*(4)*, Yield [%]
$Cr_2(SO_4)_3 \cdot 18H_2O$	63	CH_3	11	*(4a)* 48
		C_2H_5	11	*(4b)* 59
		n-C_3H_7	11	*(4c)* 60
		i-C_3H_7	11	*(4d)* 56
		n-C_4H_9	11	*(4e)* 61
		n-C_5H_{11}	11	*(4f)* 59
$Mg(ClO_4)_2$ [a]	66	n-C_4H_9	29	*(4e)* 53
$MnCl_2 \cdot 4H_2O$ [a, b]	80	n-C_4H_9	30	*(4e)* 55
—	—	n-C_4H_9	11	*(4e)* 14

[a] *(4e)* is obtained analytically pure. [b] Reaction performed in methanol.

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Procedure

Synthesis of *(4e)*: Compound *(1)* (4.32 g, 40 mmol) and $Cr_2(SO_4)_3 \cdot 18H_2O$ (7.16 g, 10 mmol) are dissolved in anhydrous ethanol (50 ml) and heated for 30 min under argon. After brief cooling, a solution of *(2e)* (6.24 g, 40 mmol) in anhydrous ethanol (10 ml) is added and the mixture is heated under reflux for an additional 11 h. After cooling the crude product is filtered off under suction, washed thoroughly with methanol, and dried. Further purification is accomplished by extraction for 16 h with toluene, in which *(4e)* dissolves with an intense green color when hot. On cooling a sample of *(4e)* is obtained (4.9 g, 61 %) which proves to be pure on thin-layer chromatography.

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(1), 1187-42-4; *(2a)*, 42588-57-8; *(2b)*, 30989-75-4; *(2c)*, 21037-71-8; *(2d)*, 30989-77-6; *(2e)*, 21037-73-0; *(2f)*, 30989-79-8; *(3)* (MX = $Cr_2(SO_4)_3$, 67784-58-1; *(3)* (MX = $Mg(ClD_4)_2$, 67784-56-9; *(3)* (MX = $MnCl_2$), 67784-54-7; *(4a)*, 67773-70-0; *(4b)*, 67773-71-1; *(4c)*, 67773-72-2; *(4d)*, 67773-73-3; *(4e)*, 67773-74-4; *(4f)*, 67773-75-5; $Cr_2(SO_4)_3$, 10101-53-8; $Mg(ClO_4)_2$, 10034-81-8; $MnCl_2$, 7773-01-5

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Synthesis of 5′-*O*-Glycosyl-*ribo*-nucleosides[**]

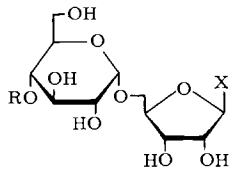
By *Frieder W. Lichtenthaler, Yuzuru Sanemitsu*, and *Toshihiro Nohara*[*]

Certain bacteria, such as *Brevibacterium ammoniagenes*[1] and *Bacillus sp. No. 102*[2], have the potential for elaborating 5′-*O*-hexosylated nucleosides of type *(1)*—*(3)*, a novel group of bacterial metabolites that can vary in the nucleobase (hypoxanthine and guanine), in the hexose portion [glucose *(1a)*, *(1b)*; maltose *(2a)*, *(2b)*; and galactose *(3a)*], and in the configuration of the intersaccharide bond (α- and β-linkage). Analogs with adenine and uracil as the aglycon, *i.e. (1c)*[3], *(3c)*[4], and *(3d)*[5], have also been obtained yet by the action of bacterial enzyme preparations on maltose and *o*-nitrophenyl α-D-galactoside and the respective *ribo*-nucleoside.

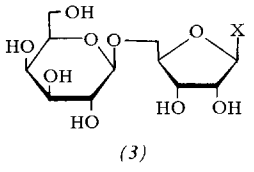
The unknown biological role of these glycosylnucleosides prompted us to embark on their chemical synthesis[6], which

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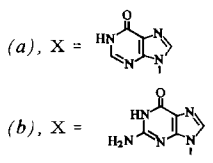
[**] Nucleosides, 35th Communication. We gratefully acknowledge support of these investigations by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 34: [7].



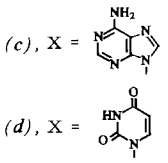
(1), R = H
(2), R = α-D-Glucosyl



(3)



(a), X =



(c), X =

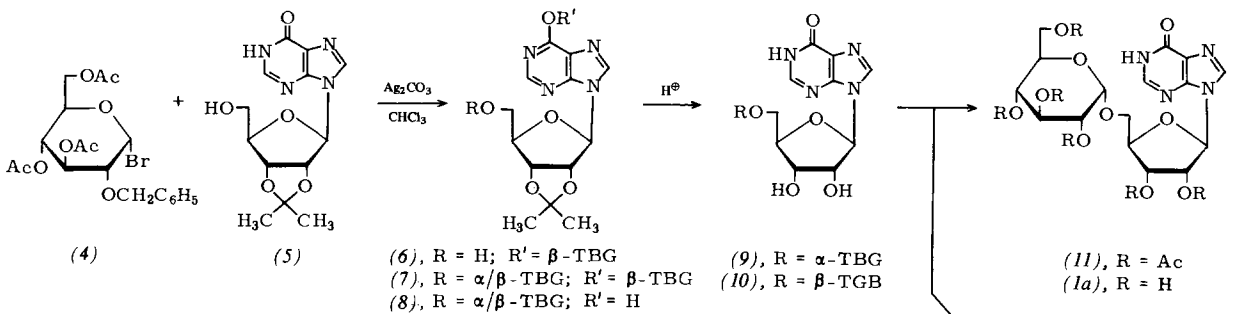
(b), X =

(d), X =

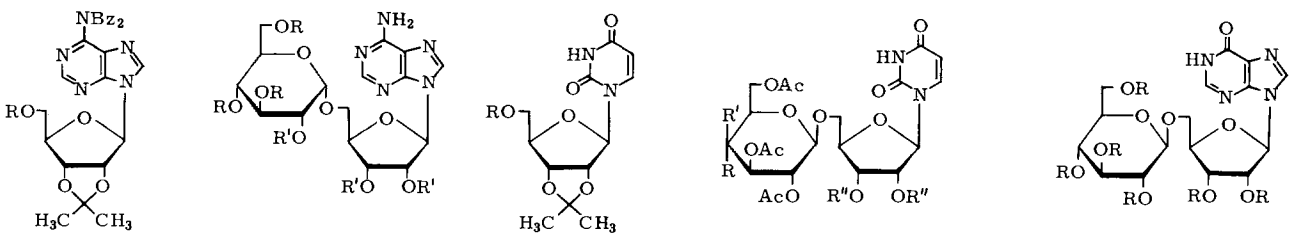
we have now completed for β-D-galactosyluridine *(3d)* and the 5′-*O*-α-D-glucosides of inosine *(1a)*, adenosine *(1c)*, and uridine *(1d)* *via* glycosylation of the respective 2′,3′-*O*-isopropylidene-nucleosides. This synthetic approach, however, is seriously impaired by fission of the *N*-glycosidic bond in purine nucleosides on glycosylation with mercuric salt type catalysts (sugar exchange reaction[7,8]), and particularly by the various nucleophilic sites of similar reactivity, whereby glycosylation can occur at the sugar hydroxyl group, at several nitrogen functions of the heterocycle as well as on oxygen in those nucleobases that contain a carboxamide function[9]. These difficulties were eventually overcome by using suitable 2′,3′-*O*-isopropylidenenucleosides protected in the heterocyclic moiety, such as the O^6-glycosylated inosine *(6)* and the N^6,N^6-bis(benzoyl)adenosine *(14)*, in which 5′-*O*-glycosylations with 2-*O*-benzylacetobromoglucose *(4)* can be effected by silver carbonate in chloroform at 60 °C.

Accordingly, on reaction of isopropylidene-inosine *(5)* with halogenose *(4)* and silver carbonate in chloroform at ambient temperature the imidoyl glucoside *(6)* is formed exclusively, which on heating (3 d, 60 °C) with an excess of *(4)* is converted into the bis(glucoside) *(7)*. In *(7)*, the imidoyl glucoside linkage is readily cleaved by treatment with 80% aqueous acetic acid (3 h, 25 °C) to give *(8)* as an approximate 3:1 mixture of α- and β-anomers. When performing the three steps *(5)* → *(6)* → *(7)* → *(8)* in one continuous operation the overall yield of *(8)* amounted to 39%. Silica gel separation of the anomers is readily effected after deacetonation[10a] to give the α-disaccharide *(9)* and its β-anomer *(10)*. For preparation of the unblocked glucosyl-inosines, *(9)* and *(10)* were first converted *via* hydrogenolysis[10b] and acetylation into their highly crystalline hexaacetates *(11)* and *(24)*. De-*O*-acetylation of *(24)*[10c] gave the 5′-*O*-(β-D-glucosyl)inosine *(25)*, which was readily hydrolyzed upon digestion with β-glucosidase, yet was unaffected by α-glucosidase treatment. Similarly, *(11)* was converted into 5′-*O*-(α-D-glucosyl)inosine *(1a)*, which was identical with the product derived from *Bacillus sp. No. 102*[11] on the basis of IR, rotation, and TLC behavior, as well as its stability towards β-glucosidase[10d] *versus* prompt hydrolysis on exposure to α-glucosidase.

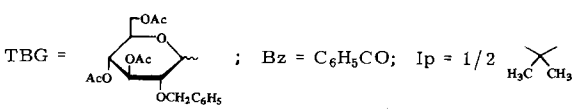
For the synthesis of adenosine glycosides the N^6,N^6-bis(benzoyl) derivative *(14)* [prepared from 2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine[12] by exhaustive benzoylation to give *(13)* and subsequent detritylation with 1% trifluoroacetic acid in dichloromethane] was subjected to silver carbonate-induced glycosylation with *(4)* (3 d, 60 °C in $CHCl_3$) to yield *(15)* as an approximately 5:1 mixture of α- and β-anomers. Removal of the minor product by silica gel chromatography was effected at the triacetate stage *(16)* (generated on acid treatment and subsequent hydrogenolysis[10a,b]) and afforded 58% [based on *(15)*] of the pure α-anomer *(16)*. Acetylation gave the hexaacetate *(17)*, deacetylation[10c] the 5′-*O*-(α-D-glucosyl)-adenosine *(1c)*, readily characterized by UV, ^{1}H-NMR, and MS data. On the basis of the scarce data available for the



(4) (5) (6), R = H; R′ = β-TBG (7), R = α/β-TBG; R′ = β-TBG (8), R = α/β-TBG; R′ = H (9), R = α-TBG (10), R = β-TGB (11), R = Ac (1a), R = H



(13), R = Trit (14), R = H (15), R = α/β-TBG (16), R = Ac; R′ = H (17), R = R′ = Ac (1c), R = R′ = H (18), R = H (19), R = α-TBG (20), R = OAc; R′ = H; R″ = Ip (21), R = OAc; R′ = R″ = H (22), R = H; R′ = OAc; R″ = Ip (23), R = R″ = Ac; R′ = OAc (24), R = Ac (25), R = H



TBG = ; Bz = C_6H_5CO; Ip = 1/2

A. niger derived *(1c)*—R_F-values relative to adenosine, hydrolysis with α-glucosidase, and stability towards β-glucosidase[3]—synthetic and natural product were identical.

Synthetic access to 5′-*O*-glycosyluridines proved to be more simple, since pyrimidine nucleosides are unable to undergo the sugar exchange reaction *via* 1,5-anhydroribose formation[7, 8], and hence allow the use of Königs-Knorr type catalysts for inducing *O*-substitution at the sugar portion. Thus, mercuric cyanide induced reaction of 2′,3′-*O*-isopropylideneuridine *(18)* with acetobromoglucose in nitromethane (3 h, 55 °C) afforded the 5′-*O*-β-glucoside *(20)* with only small amounts of the N^3,$O^{5'}$-bis-glucoside being detectable by TLC. Deacetonation[10a] gave a crystalline tetraacetate *(21)*, which was converted into 5′-*O*-(β-D-glucosyl)uridine β-*(1d)* by deacetylation. When using *(4)* for glycosylation of *(18)* under these conditions, an approximately 2:1 mixture of *(19)* and its β-anomer was obtained, which is readily separable on silica gel. Sequential deblocking[10] of *(19)* then afforded 5′-*O*-(α-D-glucosyl)uridine *(1d)*, which exhibited a positive optical rotation (Table 1) as opposed to the negative value for the β-anomer β-*(1d)*. Thus, the configuration of the intersaccharide bond in 5′-*O*-hexosylnucleosides may already be deduced from rotational data.

Table 1. Physical data and yields of glycosyl nucleosides [a].

Product	Yield [%] (Reactant)	M.p. [°C]	$[\alpha]_D^{23}$ [°] (*c*, solvent)
(6)	74 *(5)*	syrup	−46.8 (1, $CHCl_3$)
(9)	51 *(8)* [b]	syrup	+ 6.5 (0.5, $CHCl_3$)
(10)	13 *(8)* [b]	177—178	+17.0 (0.5, $CHCl_3$)
(11)	65 *(9)*	212—213	+56.9 (0.3, $CHCl_3$)
(24)	77 *(10)*	119—120	−37.1 (0.3, $CHCl_3$)
(25)	76 *(24)*	159—164	−31.2 (0.5, H_2O)
(1a)	56 *(11)*	amorphous [c]	+36.2 (0.5, H_2O)
(13)	88 [d]	151—152	−24.3 (1, $CHCl_3$)
(14)	84 *(13)*	syrup	−44.7 (0.7, $CHCl_3$)
(17)	37 *(14)* [e]	syrup	+51.4 (0.7, $CHCl_3$)
(1c)	55 *(17)*	amorphous	+33.2 (0.5, H_2O)
(20)	73 *(18)*	syrup	−18.4 (1, $CHCl_3$)
(21)	74 *(20)*	199—201	−31.4 (0.7, CH_3OH)
β-*(1d)*	54 *(21)*	217—218	−29.7 (1, DMF)
(19)	61 *(18)*	syrup	+24.6 (1, $CHCl_3$)
(1d)	54 *(19)*	208—210	+38.9 (0.6, DMF)
(22)	78 *(18)*	syrup	− 6.3 (1, $CHCl_3$)
(23)	74 *(3d)*	165—166 (dec.)	−17.2 (1, $CHCl_3$)
(3d)	55 *(22)*	223—226	−11.3 (1, DMF)

[a] Values for combustion analysis, molecular weights (MS-FD spectra), as well as UV, ^{1}H-, and ^{13}C-NMR data are in accord with the structures and configurations assigned. [b] Overall yields from *(5)* are 19 % for *(9)* and 5 % for *(10)*. [c] Softening at 145—155 °C. [d] Reactant: 2′,3′-*O*-isopropylidene-5′-*O*-trityladenosine [12]. [e] Overall yield for the steps *(14)* → *(15)* → *(16)* → *(17)*.

In similar fashion, 5′-*O*-(β-galactosyl)uridine *(3d)* was synthesized in an overall yield of 43 % by mercuric cyanide catalyzed glycosylation of *(18)* with acetobromogalactose and subsequent deblocking of *(22)*. Acetylation afforded the hexaacetate *(23)*, whose crystal form (rhombic prisms), m.p., and NMR data [1′-H at δ = 6.31 as 6 Hz-d, 1″-H at δ = 4.58 as 7 Hz-d (in $CDCl_3$)] were in good agreement with those reported for the product resulting from the action of β-D-galactosidase on *o*-nitrophenyl α-D-galactoside and uridine and subsequent acetylation[5].

The problem of a specific chemical synthesis of 5′-*O*-glycosylated purine and pyrimidine nucleosides thus appears to be solved, permitting the preparation of specifically labeled compounds of this type for unraveling their biological role. The first indications of their function come from strong inhibition of maltodextrin phosphorylase by inosine β-glucoside *(25)* [$K_i = 2 \times 10^{-4}$ mol/l at 30 °C for polysaccharide biosynthesis and 3.8×10^{-4} mol/l for maltodextrin degradation] which is competitive with glucose 1-phosphate and maltodextrin whereas the α-anomer *(1a)*, like inosine, exhibits no significant effector property[13]. Compound *(25)* is therefore a specific active site inhibitor, suggesting a role as regulator of the activity of phosphorylases or other enzymes of reserve carbohydrate metabolism.

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[10] Conditions for deblocking of the protected glycosyl-nucleosides: a) deacetonation: 5:1 trifluoroacetic acid/water for 10—15 min at 20 °C; owing to substantial hydrolysis of the intersaccharide linkage at longer reaction times, the course is to be monitored by TLC ($CHCl_3/CH_3OH$ 30:1); b) de-*O*-benzylation: hydrogenolysis with 10 % Pd/C in methanol/acetic acid (5:2); c) de-*O*-acetylation: ammonia/methanol or sodium methoxide/methanol. d) For enzymatic hydrolysis commercial α- and β-glucosidases (Boehringer Mannheim) were used under standard conditions.
[11] We are grateful to Dr. *Ikuo Nogami*, Takeda Chem. Ind., Osaka, for a sample of *Bacillus sp. No. 102* derived *(1a)*.
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[13] The inhibitor studies were performed by Prof. Dr. *D. Palm*, Physiologisch-chemisches Institut der Universität Würzburg, who kindly communicated these results.

Synthesis of a Δ^4-1,4,2λ^5-Selenazaphospholine, the First Selenophosphorane[**]

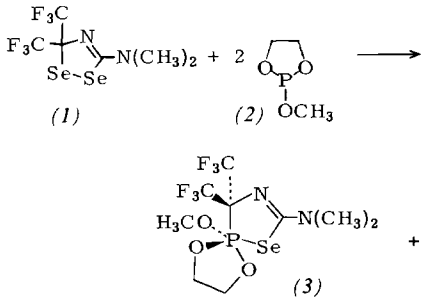
By *Klaus Burger, Ralph Ottlinger, Albin Frank*, and *Ulrich Schubert*[*]

Selenophosphoranes have been discussed as intermediates in the hydrolysis of selenophosphoric acid *O,O*-diesters[1], in the stereospecific deoxygenation of oxiranes with triphenylphosphane or tri-*n*-butylphosphane selenide[2], and in the oxidation of trivalent phosphorus with dimethylselenium oxide[3], though demonstration of their actual existence has not been reported in the literature so far.

We have now been able to prepare, to our knowledge, the first selenophosphorane by reaction of 5,5-bis(trifluoromethyl)-Δ^3-1,2,4-diselenazoline *(1)*[4] with 2-methoxy-1,3,2-dioxaphospholane *(2)* at −30 °C. The product turned out to be sensitive to hydrolysis and thermolabile.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



The spectroscopic data[5] are consistent with the structure of a Δ^4-1,4,2λ^5-selenazaphospholine *(3)*. The $^5J_{PH}$ coupling of 1.5 Hz demonstrates the presence of the structural unit P—SeCNC—H. The magnetic non-equivalence of the two trifluoromethyl groups indicated by the ^{19}F-NMR spectrum discounts involvement of irregular isomerization processes *via* open-chain dipolar species.

The downfield position of the ^{31}P-NMR signal ($\delta = -26.1$)[6] finds a parallel in the thiophosphorane series, for which δ-values up to -18 have been reported[7], and thus appears to be a chalcogen effect.

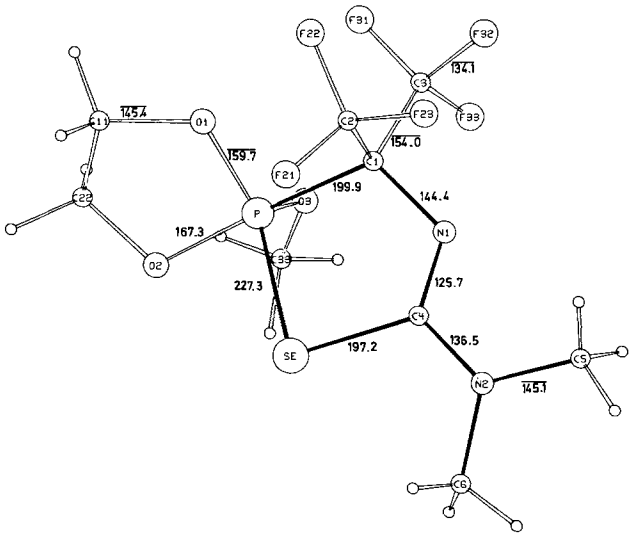


Fig. 1. Structure of compound *(3)*. Bond lengths in pm. Bond angles: C1—P—O1 87°, C1—P—O3 91°, C1—P—Se 89°, O2—P—O1 91°, O2—P—O3 99°, O2—P—Se 83°, O1—P—O3 112°, O1—P—Se 135°, O3—P—Se 111°, C1—P—O2 168°; P—Se—C4 89.9°; all other angles have the usual values.

Final confirmation of the proposed structure *(3)* was provided by an X-ray structural analysis[8] (Fig. 1). The selenazaphospholine ring skeleton is almost planar (max. deviation C1, 20 pm); the dimethylamino moiety deviates only slightly from a coplanar arrangement. The selenium atom assumes an equatorial position in the slightly distorted trigonal-bipyramidal coordination sphere of the phosphorus in which both ring systems are placed apical/equatorial. The observed P—Se bond length of 227.3(2) pm corresponds very well to the single-bond length calculated from covalent radii.

Experimental:

A solution of *(2)* (0.30 g, 2.5 mmol) in 5 ml anhydrous hexane is added dropwise under nitrogen at -30°C to a solution of *(1)*[4] (0.38 g, 1 mmol) in 5 ml of anhydrous hexane. A precipitate consisting of *(3)* and *(4)* crystallizes out, with concomitant decoloration of the reaction solution. Recrystallization of this precipitate three times from chloroform affords analytically pure 7-dimethylamino-5-methoxy-9,9-bis(trifluoromethyl)-1,4-dioxa-6-selena-8-aza-5λ^5-phosphaspiro-[4.4]non-7-ene *(3)*; yield 0.30 g (69%), m.p. 102 °C (dec.).

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(1), 67213-19-8; *(2)*, 3741-36-4; *(3)*, 67761-24-4; *(4)*, 67761-25-5

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Scope of Application of the Isoselective Relationship

By *Otto Exner* and *Bernd Giese*[*]

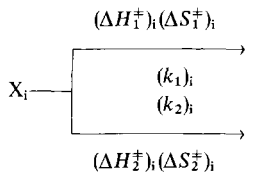
Linear relationships between activation enthalpies $\Delta H^{\neq}$ and activation entropies $\Delta S^{\neq}$ of a reaction series, the isokinetic relationships (IKR), have important applications in organic chemistry[1a], biochemistry[1b], and catalysis[1c]. Since $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are interdependent, a statistically correct treatment of the IKR with the independent variables T (reaction temperature) and $\lg k$ (reactivity) must be carried out[2]. The IKR then describes a family of Arrhenius lines intersecting in a point with the coordinates β^{-1} (β = isokinetic temperature) and y (reactivity at the isokinetic temperature) [Eq. (1)][2].

$$X_i \xrightarrow[k_i]{\Delta H_i^{\neq}\,\Delta S_i^{\neq}} \text{Products}$$

$$\lg k_{ij} = y + b_i(T_j^{-1} - \beta^{-1}) \qquad (1)$$

The subscript i signifies the reaction (*e.g.* that of the molecules X_i) and j the reaction temperature. The collection of *selectivity values* for molecules X_i of the same type of structure which fall within a small temperature range, the isoselective temperature β_{is}, has led to the concept of the isoselective relationship (ISR)[3], in which the differences in activation enthalpies $\Delta H_2^{\neq} - \Delta H_1^{\neq}$ are linearly related to the differences in activation entropies $\Delta S_2^{\neq} - \Delta S_1^{\neq}$. If the isoselective temperature does not fall in the range of measurement the validity of the ISR according to Eq. (2) can be checked analogously to Eq. (1).

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$$\lg\left(\frac{k_1}{k_2}\right)_{ij} = y + b_i(T_j^{-1} - \beta_{is}^{-1}) \qquad (2)$$

Whether isoselective relationships have the same scope of application as isokinetic relationships will be examined here using reaction series in which isokinetic relationships are valid in accordance with Eqs. (3a) and (3b).

$$(\lg k_1)_{ij} = y_1 + (b_1)_i(T_j^{-1} - \beta_1^{-1}) \qquad (3a)$$

$$(\lg k_2)_{ij} = y_2 + (b_2)_i(T_j^{-1} - \beta_2^{-1}) \qquad (3b)$$

The reactivity relationships (3a) and (3b) can be transformed by subtraction into the selectivity relationship (4).

$$\lg\left(\frac{k_1}{k_2}\right)_{ij} = y_1 - y_2 - (b_1)_i\beta_1^{-1} + (b_2)_i\beta_2^{-1} + [(b_1)_i - (b_2)_i]\,T_j^{-1} \qquad (4)$$

Eq. (4) corresponds to Eq. (2) and thus affords a relationship between the independent variables $\lg k_1/k_2$ and T (validity of the ISR) if

a) the slopes b_1 and b_2 and thus the activation enthalpies $\Delta H_1^{\neq}$ and $\Delta H_2^{\neq}$ are linearly related to each other [Eq. (5), α and c are constants]

$$(\Delta H_2^{\neq})_i = \alpha(\Delta H_1^{\neq})_i + c \qquad (5)$$

in this case the isoselective temperature $(\beta_{is})_{calc}$ can be calculated according to Eq. (6)[4]:

$$(\beta_{is})_{calc} = \frac{(\alpha - 1)\cdot\beta_1\cdot\beta_2}{\alpha\beta_1 - \beta_2} \qquad (6)$$

and/or b) if the isokinetic temperatures are equal in magnitude [Eq. (7)].

$$\beta_1 = \beta_2 = \beta_{is}$$

For seven pairs of reaction series we have calculated the isoselective temperatures from the isokinetic temperatures β_1 and β_2 using Eq. (6). In Table 1 these are compared with the isoselective temperatures β_{is} obtained applying the previously developed statistical method[2] to the isoselective relationship [Eq. (2)].

As in the discussion of isokinetic relationships[2], for assessment of the isoselective relationships the standard differences $s_{o,is}$ (calculated with assumption that the ISR is valid) and $(s_{oo})_{is}$ (calculated without additional assumption of the validity of the ISR) must be compared with each other. If $s_{o,is}$ is smaller or of similar magnitude to $(s_{oo})_{is}$ and the statistical ψ value is smaller than 0.1[11a] the existence of the ISR can be deduced from the experiments. The data given in Table 1 show that of the seven series of reactions for which the isokinetic relationships have been demonstrated, the isoselective relationship applies to only three (A, B, and G). In the case of the reaction series A and B, Eq. (5) is fulfilled very accurately, so that β_{is} is given by Eq. (6). However, also in the case of the reaction series for which the validity of the ISR cannot be deduced, Eq. (5) can be approximately applied. The mathematical analysis of reactivities thus indicates limited validity of the ISR compared to the IKR. The reason for this is that the changes in the selectivities within the small temperature range in which the reactivities could be measured are too small. A decision on the validity of the ISR should then be carried out experimentally by selective measurements which are usually possible over much greater temperature ranges than corresponding reactivity determinations.

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[3] *B. Giese*, Angew. Chem. *88*, 161 (1976); *89*, 162 (1977); Angew. Chem. Int. Ed. Engl. *15*, 174 (1976); *16*, 125 (1977).—By analogy with the isokinetic temperature β, the isoselective temperature will be designated as β_{is}.
[4] Eq. (6) is not valid for $\beta_1 = \beta_2 = 0$; in this case β_{is} is likewise equal to zero.

Table 1. Statistical evaluation of reaction series for the determination of isoselective relationships (temperatures in K).

Reaction series, Ref.			β_1 [a] / β_2	β_{is} / $(\beta_{is})_{calc}$	$10^4 \times$ $s_{o,is}$ / $(s_{oo})_{is}$	r [b]	ψ	Validity of ISR
A [5]	Solvolysis of 4-$BrC_6H_4NHCH_2C(NO_2)_2C_6H_4X$	in H_2O	322	269	23	0.9999	0.0045	+
		in CH_3OH	4159	(269)	(22)			
B [5]	Solvolysis of $XC_6H_4NHCH_2C(NO_2)_2C_6H_4$-4-$NO_2$	in H_2O	474	491	93	0.9999	0.020	+
		in CH_3OH	781	(492)	(103)			
C [6]	Solvolysis of $C_6H_5SO_3R$	in CH_3OH	−780 [c]	487	186	0.9951	0.12	−
		in i-C_3H_7OH	−733 [d]	(−2078)	(61)			
D [7]	Reactions of 2-bromoesters	with pyridine	97 [e]	543 [e]	263	0.9829	0.34	−
		with aniline	1 [e]	(893)	(322)			
E [8]	Reactions of 2-bromoketones	with pyridine	−691	−211 [d]	225	0.9987	0.23	−
		with aniline	−805	(2322)	(252)			
F [9]	Reaction of substituted benzoic acids	with diphenyldiazomethane	1552 [e]	514 [d]	376	0.999	0.34	−
		with dinitrodiphenyldiazomethane	92950 [d]	(510)	(286)			
G [10]	Diels-Alder reactions of substituted styrenes	with dinitrophencyclone	−41800 [c]	−428	84	0.9659	0.014	+
		with dimethoxyphencyclone	3466 [c]	(−2090)	(95)			

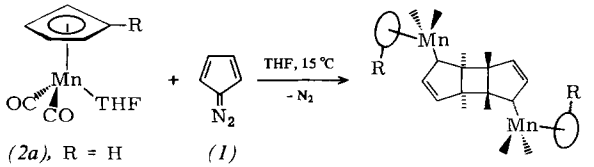
[a] Calculated by the least squares method [2].
[b] Correlation coefficient of Eq. (5).
[c] Possibly an isoentropic reaction series; $\beta = \infty$ cannot be ruled out.
[d] This reaction series can be either isoentropic or isoenthalpic; neither $\beta = \infty$ nor $\beta = 0$ can be ruled out.
[e] Possibly an isoenthalpic series; $\beta = 0$ cannot be ruled out.

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Synthesis of Carbocyclic Carbene Complexes by Metal-Induced Diazocyclopentadiene Fragmentation[1]

By *Wolfgang A. Herrmann, Johann Plank, Manfred L. Ziegler,* and *Klaus Weidenhammer*[*]

η^1- and η^5-Halocyclopentadienyl-metal complexes which are otherwise accessible only by multistep reactions, if at all, can be prepared from diazocyclopentadiene *(1)*[2] in a reaction involving halogen transfer from the metal to the carbon atom which originally carried the N_2 substituent[3]. On attempted preparation of cyclopentadienylidene complexes by metal-induced fragmentation of *(1)*, by analogy with earlier work on acyclic diazoalkanes[3], we observed formation of a transition-metal stabilized oligocyclic carbene for the first time:



(2a), R = H
(2b), R = CH_3

(1)

(3a, b)

The action of an excess of diazocyclopentadiene *(1)* on tetrahydrofuran solutions of the manganese complexes *(2a)* and *(2b)* at 10 to 25 °C leads, by way of slow evolution of nitrogen and black coloration of the reaction mixture, to the diamagnetic compounds *(3a)* and *(3b)*, respectively, which were shown by complete elemental analysis, osmometric molecular-weight determination, and IR and mass spectra to be dimers of the expected carbene derivatives $(\eta^5\text{-}RC_5H_4)Mn(CO)_2(\sigma\text{-}C_5H_4)$. Since the NMR spectra did not permit unequivocal determination of structure we have performed an X-ray structure analysis on *(3b)*[4]. The surprising result of this study was that the molecular units dimerize by a [2+2]cycloaddition of the cyclopentadienylidene systems. The novel tricyclic $C_{10}H_8$ dicarbene formed in this way spans two $(\eta^5\text{-}RC_5H_4)Mn(CO)_2$ units, the *anti* configuration of the bridging ligand giving rise to the centrosymmetry of the molecule. The planar central four-membered ring (±0.004 pm) makes angles of 110.3° with the best planes (±1 pm) of the two annelated five-membered rings.

The remarkably high thermal stability of the complexes *(3a)* and *(3b)* is due to conjugation of the manganese-carbene bonds with the vinylic double bonds in the bridging ligand system. This conjugation is manifested in the short Mn—C(carbene) distances of 187.8(8) pm[5] and the significant shortening of the C(1)—C(5) and C(1′)—C(5′) distances relative to those of typical single bonds.

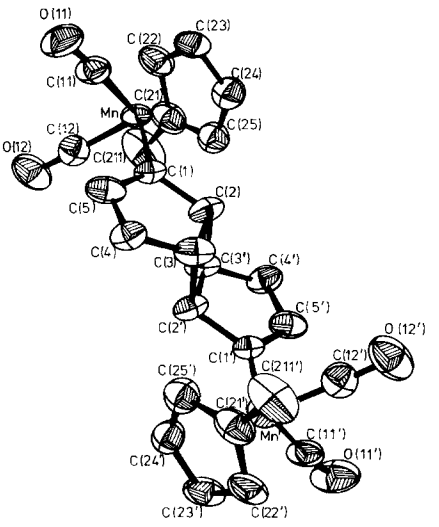


Fig. 1. ORTEP plot of the dinuclear manganese complex *(3b)* having a tricyclic dicarbene bridge. The thermal ellipsoids correspond to a probability of 50 %.

Bond lengths [pm]		Angles [°]	
C(1)—C(2)	153.0(14)	C(1)—C(5)—C(4)	112.5(1.0)
C(1)—C(5)	146.0(15)	C(2)—C(3)—C(4)	103.4(8)
C(2)—C(3)	157.4(13)	C(3)—C(4)—C(5)	111.2(9)
C(2)—C(3′)	159.6(13)	C(3)—C(2)—C(3′)	88.3(6)
C(3)—C(4)	153.0(17)	Mn—C(1)—C(5)	126.8(7)
C(4)—C(5)	136.7(14)		
Mn—C(1)	187.8(8)		

Procedure[6]:

$(\eta^5\text{-}RC_5H_4)Mn(CO)_3$ (10 mmol, 2.04 and 2.18 g, respectively) is dissolved in THF (200 ml) and irradiated in a Pyrex immersion well apparatus at 10 °C until evolution of gas ceases (Hg high-pressure lamp, TQ 150/Z1). A 0.1 M solution of *(1)* in benzene (100 ml) is added dropwise to the resulting solution of *(2a)* or *(2b)*. After 12 hours' stirring at 25 °C the dark brown oily crude product is chromatographed on 60 × 2.4 cm SiO_2 (Merck, 0.063—0.200 mm, activity II—III, 15 °C), the dicarbene complex *(3a)* or *(3b)* being eluted with benzene as a dark brown zone that is slightly air-sensitive. After evaporation *in vacuo* the eluate is stirred with *n*-pentane (50 ml), the precipitated dark brown powder is filtered over a G 3 frit, washed twice with *n*-pentane (2 × 10 ml), and crystallized from dichloromethane/diethyl ether (2:1) at −35 °C. The product forms black air-stable crystals which are soluble in benzene and polar organic solvents. Yield 504 mg of *(3a)* (21 %) and 508 mg of *(3b)* (20 %).—IR: νCO [$CHCl_3$; cm^{-1}] *(3a)* 1965 vs, 1900 vs; *(3b)*: 1963 vs, 1897 vs; νC=C [KBr; cm^{-1}]: *(3a)* 1517 m, *(3b)* 1520 m.

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[4] Compound *(3b)* crystallizes monoclinically in the space group $C_{2h}^5\text{-}P2_1/n$, with $a = 1123.9(6)$, $b = 1107.4(3)$, $c = 897.5(3)$ pm, $\beta = 93.49(6)°$; $Z = 2$. 1352

independent nonzero reflections were collected with an automatic Siemens single crystal diffractometer and corrected in the usual way ($R = 7.6\,\%$).

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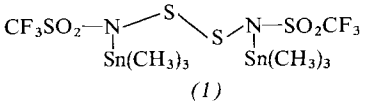
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A Cyclotetra(azadithiane)—The First Twelve-Membered Sulfur-Nitrogen Ring[**]

By *Bernt Krebs, Michael Hein, Manfred Diehl*, and *Herbert W. Roesky*[*]

The largest previously reported sulfur-nitrogen ring[1] containing sulfur atoms of coordination number 2 is the ten-membered S_5N_5 cation[2]. It is clear that large SN rings such as this can be synthesized only in the form of their cations or carrying electron-attracting substituents; otherwise strong transannular interactions favor the formation of smaller rings. We have now found that the trifluoromethanesulfonyl group is suitable as electron-attracting substituent for this purpose. Thus, the diaminodisulfane *(1)*, prepared from S_2Cl_2 and $CF_3SO_2N(SnMe_3)_2$ reacts with further dichlorodisulfane in dichloromethane to give the novel S_8N_4 ring *(2)*:

$$2\,CF_3SO_2N[Sn(CH_3)_3]_2 + S_2Cl_2 \xrightarrow[-2(CH_3)_3SnCl]{}$$



(1)

$$2\,(1) + 2\,S_2Cl_2 \xrightarrow[-4(CH_3)_3SnCl]{} S_8N_4(SO_2CF_3)_4$$

(2)

The mass spectrum of *(2)* contains the molecular ion at $m/e = 844$ (rel. int. 1 %) and the fragment NS_2^+ at $m/e = 78$ (100 %). In the ^{19}F-NMR spectrum only one signal is observed at $\delta = 79.2$ ($CFCl_3$ ext.). An X-ray structural analysis of *(2)* [monoclinic, space group $C2/c\text{-}C_{2h}^6$; $a = 16.715(3)$, $b = 7.377(2)$, $c = 22.420(4)$ Å, $\beta = 104.39(3)°$; $Z = 4$; $R = 3.8\,\%$] shows that the twelve-membered ring has a chair configuration (molecular symmetry $C_i\text{-}\bar{1}$) and contains four S—N—S units coupled *via* S—S bonds (2.006—2.009(1) Å). In this configuration interaction of the lone pairs is smallest. The S—N bond lengths are 1.724—1.732(3) Å in the ring and those between the N-atoms and sulfonyl groups 1.650—1.657(3) Å. The dihedral angles NSS/SSN have values of 91.3 and 94.1°.

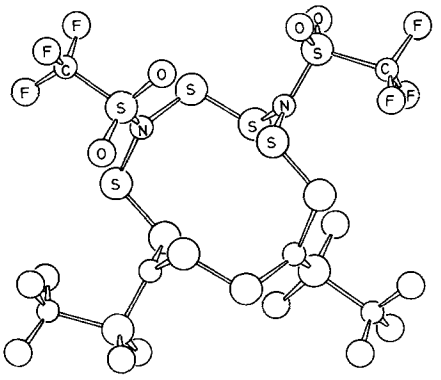


Fig. 1. Structure of the fourfold CF_3SO_2-substituted cyclotetra(azadithiane) derivative *(2)* in the crystal.

Experimental

A solution of S_2Cl_2 (1.35 g, 0.01 mol) in CH_2Cl_2 (20 ml) is added slowly with stirring to a suspension of $CF_3SO_2N(SnMe_3)_2$ (4.75 g, 0.01 mol) in 30 ml CH_2Cl_2. Compound *(1)* precipitates out, but is redissolved on further addition of S_2Cl_2. On completion of addition of S_2Cl_2 the reaction mixture is stirred for *ca.* 12 h, whereupon a product mixture $(CF_3SO_2NS_2)_n$ precipitates. The solvent and any Me_3SnCl are removed under vacuum and the residue washed with benzene. Ring compounds having $n < 4$ are then removed by sublimation at 140 °C/0.01 torr. Extraction of the remaining residue with CH_2Cl_2 and recrystallization from CH_2Cl_2 yields 0.68 g (32 %) 3,6,9,12-tetrakis(trifluoromethanesulfonyl)cyclotetra(azadithiane) *(2)*, m. p. 213—215 °C (decomp.).

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A New Cationic Mono-Hydride-Bridged Binuclear Platinum(II) Dihydride[**]

By *Gustav Bracher, David M. Grove, Luigi M. Venanzi, Fiorella Bachechi, Pasquale Mura*, and *Luigi Zambonelli*[*]

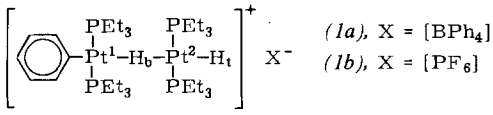
There have recently been reports of various types of dinuclear platinum hydrides[1–3]. In all instances where a monohydride-bridge has been postulated bidentate donor ligands have also been present and it has been suggested that such ligands may to a large extent influence the formation of such compounds[2].

During the reaction of *trans*-$[PtH(NO_3)(Et_3P)_2]$ with $Na[BPh_4]$, which was reported to give $[PtPh_2(Et_3P)_2]$[4], we noticed the formation of a new complex which was isolated and characterized by NMR as having the schematic structure *(1a)*. To facilitate interpretation of the aromatic region of the ^{1}H-NMR spectrum of the cationic species, the $[BPh_4]^-$ ion was exchanged with $[PF_6]^-$ to afford *(1b)*. Both *(1a)* and *(1b)* are white air-stable solids which decompose only slowly in solution.

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The hydride region of the ^{1}H-NMR spectrum of *(1b)* shows two complex multiplets with associated ^{195}Pt satellites [$(CD_3)_2CO$, 360 MHz: $\delta H_t = -11.45$, $^1J_{HPt(2)} = 1148$ Hz, $^3J_{HPt(1)} = 108$ Hz; $\delta H_b = -9.46$, $^1J_{HPt(1)} \simeq {}^1J_{HPt(2)} \simeq 500$ Hz]. The satellite structure of the two sets of signals in the ^{31}P-NMR spectrum [$(CD_3)_2CO$: $\delta = 19.0$, $^1J_{PPt} = 2591$ Hz, $^3J_{PPt} = 12$ Hz; $\delta = 8.2$, $^1J_{PPt} = 2629$ Hz, $^3J_{PPt} = 13$ Hz] provides further evidence for the binuclear structure. This was uniquely verified by a ^{195}Pt-NMR study on *(1b)* which revealed two sets of resonances ($J_{PtPt} = 366$ Hz). Interestingly, although both a bridging and terminal hydride are present in the same molecule, there is no spectroscopic evidence for a hydride-exchange process on the NMR time scale at room temperature.



(1a), X = $[BPh_4]$
(1b), X = $[PF_6]$

To date there has only been one reported X-ray crystallographic determination of a binuclear platinum hydride[3] and this fact coupled with the completely novel nature of our complex prompted us to undertake such a study on *(1a)*[5]. The overall molecular geometry of the cation, with some relevant bond lengths and interbond angles, is shown in Figure 1.

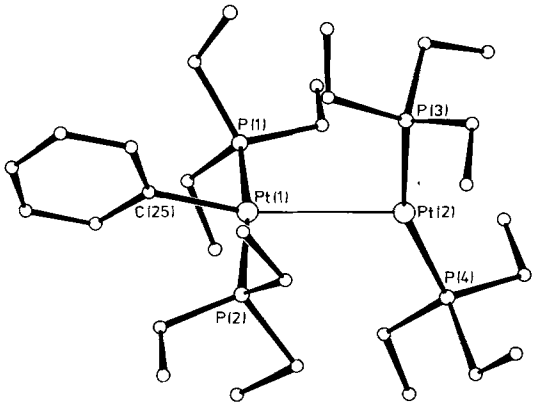


Fig. 1. Molecular Structure of $[Pt_2H_2(C_6H_5)\{P(C_2H_5)_3\}_4]^+$. Bond lengths: Pt1—Pt2 3.09, Pt1—P1 2.29, Pt1—P2 2.31, Pt1—C25 2.02, Pt2—P3 2.26, Pt2—P4 2.30 Å; Interbond angles: P1—Pt1—Pt2 93.7, P1—Pt1—P2 169.4, P1—Pt1—C25 87.8, P2—Pt1—Pt2 93.0, P2—Pt1—C25 87.9, C25—Pt1—Pt2 164.3, Pt1—Pt2—P3 91.1, Pt1—Pt2—P4 112.0, P3—Pt2—P4 156.8°; Torsion angles: P1—Pt1—Pt2—P3 87.4, P1—Pt1—Pt2—P4 −90.4, P2—Pt1—Pt2—P3 −100.6, P2—Pt1—Pt2—P4 81.6°.

Although the two hydride atoms, indicated by the spectroscopic data, have not been located at the present stage of refinement, their positions may be inferred from the X-ray data. On this basis the bridging hydride H_b lies approximately *trans* to C(25) and the terminal hydride H_t is then situated on Pt(2) approximately *trans* to H_b. The large Pt—Pt separation (3.09 Å) is consistent with a *single* hydride-bridge[3, 6] and the C(25)Pt(1)Pt(2) angle of 164.3°, probably the most important structural feature, indicates that H_b is not collinear with the two metal centers. This geometrical arrangement appears to be characteristic of compounds containing the M—H—M moiety[6]. It is also noteworthy that the plane containing P(3), Pt(2) and P(4) makes an angle of *ca.* 85° with the approximate coordination plane of Pt(1).

Compound *(1)* on addition of chloride ion undergoes a simple reversible cleavage reaction,

$$\underset{(1)}{[Pt_2H_2(Ph)(Et_3P)_4]^+} + Cl^- \rightleftharpoons \underset{(2)}{trans\text{-}[PtHCl(Et_3P)_2]} + \underset{(3)}{trans\text{-}[PtH(Ph)(Et_3P)_2]}$$

as evidenced by ^{31}P and ^{1}H-NMR spectral studies. The complex *(3)* was assigned the structure shown on the basis of its NMR data [^{31}P-NMR, $(CD_3)_2CO$: $\delta = 17.3$, $^1J_{PPt} = 2796$ Hz; ^{1}H-NMR (hydride), $(CD_3)_2CO$, 360 MHz: $\delta_H = -7.05$, $^1J_{HPt} = 648$ Hz, $^2J_{HP} = 19$ Hz]. This previously unreported compound is stable in the reaction mixture but attempts at isolating it pure from this mixture (or from the reaction of *trans*-$[PtHCl(Et_3P)_2]$ *(2)* with PhLi where it is also formed) have so far proved unsuccessful. The reactivity of *(1)*, *(3)* and related hydrides is now being investigated.

Experimental

Synthesis of *(1a)*: 500 mg (1 mmol) *trans*-$[PtH(NO_3)(Et_3P)_2]$ and 680 mg (2 mmol) $Na[BPh_4]$ were dissolved in 15 ml MeOH and the solution stirred at room temperature for 16 h. The white precipitate was separated from the yellow solution and recrystallized from $CHCl_3$/MeOH to give *(1a)*. Yield 410 mg (64 %).

Synthesis of *(1b)*: 1.261 g (1 mmol) *(1a)* was dissolved in a minimum of acetone and $NH_4[PF_6]$ added with stirring until no further precipitate of $Li[BPh_4]$ appeared to be formed. The solid was filtered off and further $NH_4[PF_6]$ added to ensure complete removal of $[BPh_4]^-$ ion from the solution. After refiltering, the solution was evaporated to dryness and the complex *(1b)* was extracted with CH_2Cl_2. Concentration of this solution and the addition of MeOH afforded crystalline *(1b)*. Yield 750 mg (70 %).

(1a) with Cl^-. 200 mg of *(1a)* was dissolved in 1 ml of $[D_6]$ acetone and LiCl added until no more would dissolve. The solution was filtered directly into an NMR tube and the product mixture *(2, 3)* measured. After removal of the solvent *in vacuo* and extraction with $CHCl_3$ (to separate LiCl) *(1a)* was retrieved almost quantitatively.

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(1a), 67891-25-2; *(1b)*, 67920-92-7; *(2)*, 16842-17-4; *(3)*, 67891-26-3; *trans*-$[PtH(NO_3)(Et_3P)_2]$, 19582-28-6

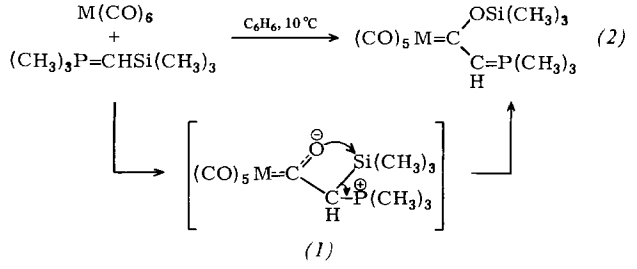
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Trimethylphosphoranediyl- and -arsoranediylmethyl-(trimethylsiloxy)carbene Complexes by 1,3-Silyl Shift[**]

By *Wolfgang Malisch, Herbert Blau,* and *Siegfried Voran*[*]

Transition metal coordinated CO ligands are usually attacked by carbanionic nucleophiles at the carbon atom[1]. In the case of phosphorus ylides there is only indirect evidence of such an attack, since the primary metalcarbonyl-ylide adduct is immediately deprotonated by further ylide to give the acyl metalate[2].

We have now found that reaction with the silyl-substituted ylide $(CH_3)_3P{=}CHSi(CH_3)_3$ takes a very different course: On starting with hexacarbonyl compounds of chromium, molybdenum and tungsten, *neutral* carbene-pentacarbonyl-metal complexes of type *(2)*, whose carbene carbon atom bears a trimethylphosphoranediylmethyl- and a trimethylsiloxy-group as substituents, are formed *directly* and *quantitatively.*

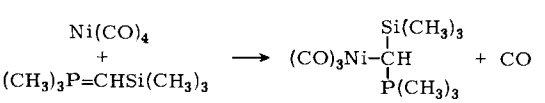


(a), M = Cr; *(b)*, M = Mo; *(c)*, M = W

In accord with this mode of product formation—to be regarded formally as addition of the ylide fragments $(CH_3)_3P{=}CH$ and $Si(CH_3)_3$ to a CO ligand—the zwitterionic adduct *(1)* generated by initial carbanion attack is not stabilized, as in other cases, by transylidation, but by transfer of the silyl group to the negatively charged acyl oxygen. The 1,3-silyl shift leading to regeneration of the ylide function proceeds so rapidly that *(1)* is neither isolable under the reaction conditions (10 °C) nor detectable by NMR spectroscopy at low temperatures (−30 °C)[3]. Accordingly the carbon bound silyl group in *(1)* displays extraordinary mobility, due to the possibility of formation of the stable Si—O bond[4].

The pale-yellow, readily crystallizable carbene complexes *(2)* are stable under N_2, but rapidly decompose in solution to, *inter alia*, $M(CO)_6$ and hexamethyldisiloxane. The composition and structure of the complexes have been confirmed by analytical and spectroscopic findings. The ^{1}H-NMR and ^{13}C-NMR spectra show, respectively, the signal of the ylide proton and of the carbene carbon as doublets with characteristic splitting ($^2J_{HCP}$ = 34 Hz; $^2J_{CCP}$ = 10 Hz) at lowest field (δH = 4.7; δC = 250). The presence of the C—O, P—C, and Si—O bonds follows from the position of the stretching absorptions at 1062 (vs), 968 (s), and 752 (m) cm^{-1}. The pentacarbonyl structure is proved from the νCO bands, which indicate both high steric demand and high σ-donor/π-acceptor ratio for the ylide carbene ligand (5 IR-active νCO, low wavelengths).

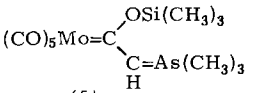
While, analogously to the $M(CO_6)$ reaction, $Fe(CO)_5$ and the silyl ylide afford the complex $(CO)_4FeC[OSi(CH_3)_3]$—$CH{=}P(CH_3)_3$ *(3)*, which is trigonal bipyramidal configurated and bears the carbene ligands in the axial position [local C_{3v} symmetry; νCO: 2020 (s) $A_1^{(2)}$, 1939 (s) $A_1^{(1)}$, 1908 (vs) E][5], $Ni(CO)_4$ affords the *ylide complex (4).*



(4)

This different mode of reaction is rationalized in terms of the high exchange activity of $Ni(CO)_4$[6] and low electrophilicity of its CO ligands[7].

The direct conversion of complex-bound carbon monoxide into a ylide carbene ligand according to the simple principle of silyl-ylide addition/1,3-silyl shift presented here also occurs with $(CH_3)_3As{=}CHSi(CH_3)_3$. On reaction with $Mo(CO)_6$ in benzene at 25 °C we obtained the first (arsenic ylide)carbenemetal complex *(5)*, m.p. 71—73 °C, which exhibits the same spectral characteristics as *(2b)*. Moreover, its ^{1}H-NMR spectrum (in benzene) recorded at room temperature demonstrates the existence of two isomers attributable to hindered rotation about the $C_{carbene}$—C_{ylide} bond.



(5)

Procedure

All operations must be carried out under N_2 using oxygen-free solvents.

A solution of $(CH_3)_3P{=}CHSi(CH_3)_3$[8] (0.85 g, 5.2 mmol) in benzene (10 ml) is added dropwise at 10 °C to a suspension of $Cr(CO)_6$ (1.15 g, 5.2 mmol) in benzene (20 ml). After 30 minutes' stirring the clear yellow solution is concentrated by evaporation to 10 ml and *(2a)* is precipitated by addition of 20 ml pentane; recrystallization from benzene/pentane (1 : 2) at −15 °C affords pale yellow crystals, m.p. 91—93 °C, yield 1.71 g (86 %).—*(2b)*: m.p. 112—114 °C (88 %); *(2c)*: m.p. 118—120 °C (84 %).

Using the same procedure, reaction of $Fe(CO)_5$ (0.39 g, 2.0 mmol) with $(CH_3)_3P{=}CHSi(CH_3)_3$ (0.32 g, 2.0 mmol) affords pale-pink crystalline *(3)*; yield 0.65 g (91 %), m.p. 42—44 °C.

Spectroscopic data of (2a): ^{1}H-NMR (in C_6D_6, TMS int.): δCH$_3$P = 0.6 (d, 9H), $^2J_{HCP}$ = 13.4 Hz; δCH$_3$Si = 0.44 (s, 9H); δCH=P = 4.78 (d, 1H), $^2J_{HCP}$ = 34.2 Hz.—^{13}C{^{1}H}-NMR (in C_6D_6, TMS int.): δCH$_3$P = 11.3, J_{CP} 57.3 Hz; δCH$_3$Si = 2.1; δC_{ylide} = 94.7, J_{CP} = 67.6 Hz; δCO_{cis} = 211.6; δCO_{trans} = 222.0; δ$C_{carbene}$ = 250.9, $^2J_{CCP}$ = 10 Hz.—^{31}P{^{1}H}-NMR (in C_6D_6, H_3PO_4 ext.): δ = −11.8.—IR (ν_{CO} in C_6H_6): 2035 (w) $A_1^{(2)}$, 1951 (vw) B_1, 1915 (s) E, 1902 (s) E, 1897 (m) $A_1^{(1)}$ cm^{-1}.

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Dichlorocarbene Complexes of Iron(II)-Porphyrins—Crystal and Molecular Structure of Fe(TPP)(CCl_2)(H_2O)

By *Daniel Mansuy, Marc Lange, J. C. Chottard, J. F. Bartoli, Bernard Chevrier*, and *Raymond Weiss*[*]

We recently reported that the reaction of *meso*-tetraphenylporphyrinatoiron(II) (Fe(TPP)) with carbon tetrachloride in the presence of an excess of reducing agent leads to the formation of a complex, for which we proposed the dichlorocarbene complex structure Fe(TPP)(CCl_2) on the basis of elemental analysis, and spectral data[1]. Since it was the first example of a dihalogenated carbene complex of a transition metal and the first isolated carbene complex of a metalloporphyrin, the latter point bringing valuable evidence in favor of the formation of such a CCl_2 complex of hepatic cytochrome P 450, after carbon tetrachloride metabolization[2], it appeared to us most important to prove the Fe—CCl_2 structure. We have now carried out an X-ray structure analysis, which, despite low accuracy due to crystal disorder, unequivocally confirms the proposed structure.

Single crystals for X-ray examination were obtained by slow evaporation, under argon, from a chloroform/DMF/H_2O solution of the solid previously obtained and described as Fe(TPP)(CCl_2)[1]. The compound crystallizes with a water molecule completing the coordination of the metal and with two molecules of dimethylformamide present as uncomplexed solvent of crystallization.

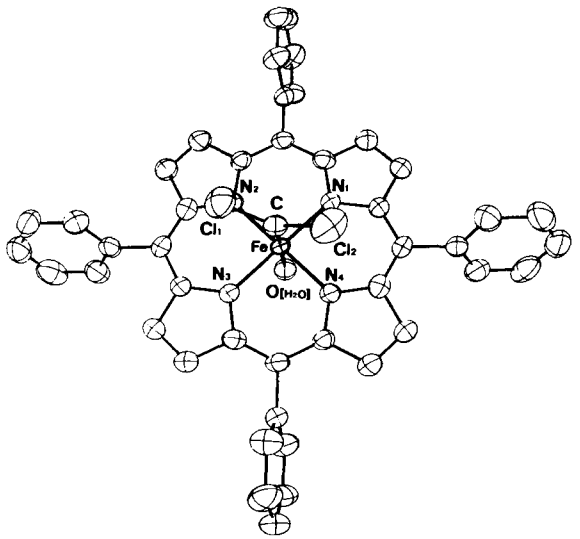


Fig. 1. Crystal structure of Fe(TPP)(CCl_2)(H_2O)·2 DMF (solvate molecule not shown). Crystal data: triclinic P1 or $P\bar{1}$: $a = 11.969(8)$, $b = 10.521(7)$, $c = 10.163(7)$ Å; $\alpha = 101.48(8)$, $\beta = 106.20(8)$, $\gamma = 107.52(8)°$; $U = 1114.6$ Å^3; $Z = 1$; $\rho_{calcd} = 1.364$, $\rho_{obsd} = 1.36$ g·cm^3 (by flotation in aqueous zinc chloride solution); MoKα radiation; 3105 independent reflections with $I > 3\sigma(I)$; anisotropic refinement; present $R = 0.085$.—Initially the structure was solved in the non-centrosymmetric space group P1. But structure refinement led us to assume that the correct space group is the centrosymmetric $P\bar{1}$. Then the molecule has crystallographically imposed $\bar{1}$ symmetry and hence the CCl_2, O(H_2O) and dimethylformamide groups are disordered. In a first approximation, the disordered groups were included with occupancy factors of 0.5.

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Figure 1 is a computer-drawn model, in perspective, of one Fe(TPP)(CCl_2)(H_2O)·2 DMF molecule as it exists in the crystal.

The overall deviations from planarity of the porphyrin core are very small (±0.03 Å). The planes of the phenyl groups are each rotated nearly 10—20° from the perpendicular to the mean plane of the porphyrin core. The iron atom is not significantly displaced from this plane. The averaged length of the equivalent Fe—N bonds (1.984(4) Å) and the distances within the porphyrin core are in good agreement with those reported for the other low-spin iron porphyrins[3]. The Fe—C (1.83(3) Å) and Fe—O(H_2O) bonds (2.13(3) Å) are essentially collinear, the C—Fe—O(H_2O) bond angle being 177.1(1.5)°[4]. The sum of the angles at the coordinated carbon is 359.2(1.0)° (sp^2 type). The C—Cl bond distances are 1.76(3) Å and the plane defined by the Fe, C, Cl_1 and Cl_2 atoms is practically perpendicular to the mean plane of the porphyrin core (87.6°). The coordinated water molecule forms hydrogen bonds to the oxygen atoms of both dimethylformamide solvate molecules (O...O distances of about 2.7—2.8 Å).

The crystallization of Fe(TPP)(CCl_2)[1] in anhydrous noncoordinating solvents (chloroform or benzene and hexane) leads to the pentacoordinated complex Fe(TPP)(CCl_2) *(1)*, while in the presence of a ligand L the hexacoordinated complexes Fe(TPP)(CCl_2)(L) *(2)* are formed. In solution, *(1)* and *(2)* are in equilibrium:

$$\underset{(1)}{\text{Fe(TPP)(CCl}_2\text{)}} + \text{L} \rightleftharpoons \underset{(2)}{\text{Fe(TPP)(CCl}_2\text{)(L)}}$$

(a), L = CH_3OH; *(b)*, L = C_2H_5OH; *(c)*, L = THF; *(d)*, L = pyridine; *(e)*, L = *N*-methylimidazole

The IR spectrum (KBr pellet or Nujol mull) of *(1)* exhibits a band at 872 cm^{-1}. This band, which is absent in the IR spectrum of Fe(TPP)($py)_2$ or Fe(TPP)(CO)(py), and which is shifted to 841 cm^{-1} in the spectrum of the Fe(TPP)($^{13}CCl_2$) complex (prepared with 95% enriched $^{13}CCl_4$), is assigned to a C—Cl stretching vibration. In the spectra of the crystalline complexes *(2a)*, *(2b)* and *(2c)* the νC—Cl band is shifted to 863 cm^{-1}. Upon heating to 100 °C/10^{-2} torr or upon recrystallization from chloroform/hexane, the complexes *(2)* are transformed into complex *(1)*. This accords with coordination of L on the iron atom *trans* to the carbene ligand[5]. This coordination is supported by the ^{1}H-NMR spectrum of *(2b)* in $CDCl_3$ solution, which evidences the one to one ratio of porphyrin and ethanol. At 34 °C, the signals of free ethanol appear; lowering the temperature to −65 °C shifts the methylene quartet and methyl triplet upfield by about $\Delta\delta \approx 1$ and 0.6 ppm[6]. Further addition of excess ethanol causes a downfield shift of the signals. These data are indicative of a rapid exchange, on the NMR time scale, between coordinated and free ethanol, the equilibrium being almost totally displaced to the left at 34 °C, when established from pure complex *(2b)*, but progressively driven to the right upon cooling.

The existence of the equilibrium is further supported by the IR spectra of *(1)* in solution, a νC—Cl vibration being observed at 872 cm^{-1} in benzene and at 863 cm^{-1} in 90:10 benzene/ethanol mixture [*(1)* → *(2)*]. The progressive addition of a ligand L to a benzene solution of complex *(1)* can be followed by visible spectroscopy. For instance, there is a gradual transformation, with isosbestic points at 413, 496 and 535 nm, of the characteristic spectrum of complex *(1)* into that of complex *(2b)* (λ = 419 and 538 nm) upon addition of ethanol.

The affinity of ethanol ($K_1 = 41$ mol^{-1} at 25 °C) and of other alcohols or tetrahydrofuran for complex *(1)* is low ($K_1 \approx$ 3—10 l mol^{-1} at 25°). Nitrogenous ligands have much higher

affinities (pyridine: $K_1 = 3500\,l\,mol^{-1}$[1]; *N*-methylimidazole: $K_1 = 75000\,l\,mol^{-1}$, each at 25 °C)[7].

Though unstable in the presence of good nucleophiles[7], and slowly oxidized in aerated solvents[1], complex *(1)* exhibits a very strong Fe—CCl_2 bond, for, as a solid, it remains unchanged when heated for one hour at 200 °C/10^{-2} torr, and in deaerated 10^{-8} M solutions it does not display any significant dissociation (as shown by visible spectroscopy).

Similar CCl_2 complexes[8] are obtained with the iron(II) complexes of *p*-methyl- and *p*-chloro-TPP, octaethylporphyrin, deuteroporphyrin dimethyl ester[9] and protoporphyrin IX.

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[8] Characterized by λ (benzene) = 409 ($\varepsilon = 2\cdot10^5$), 525 ($1.5\cdot10^4$), 555 nm (sh); 409 ($2\cdot10^5$), 525 ($1.5\cdot10^4$), 555 nm (sh); 390 ($1.3\cdot10^5$), 524 ($8\cdot10^3$), 553 nm ($1.6\cdot10^4$); 390 ($1.22\cdot10^5$), 521 ($9\cdot10^3$), 549 nm ($1.8\cdot10^4$) [9]; λ (DMF) = 414 ($1.55\cdot10^5$), 537 ($1.55\cdot10^4$), 570 nm ($1.95\cdot10^4$).

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ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

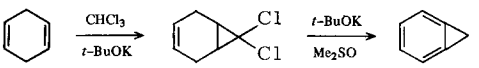
Applications of pulse radiolysis to chemical research are dealt with in a review article by *J. H. Baxendale* and *M. A. J. Rodgers*. The events which occur in an aqueous solution after the absorption process and before the participation of a dissolved compound in chemical reaction are as follows: ionization by photons or excitation or ionization by fast electrons; ion-molecule reactions with the solvent; thermalization of electrons; solvation of electrons and cations; chemical reactions (after onset of diffusion). In the chemically important final stages the following reactions take place:

$$H_2O \rightarrow H_2O^+ + e^-$$
$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH$$
$$H_2O \rightarrow H + OH$$

The most important reactive species are found to be OH and e^-, which is rapidly hydrated to e^-_{aq}. The topics studied include reduction and oxidation reactions of inorganic compounds, reactions of electrons in liquids, the solution chemistry of radical ions, and reactions of radicals. [Contributions of Pulse Radiolysis to Chemistry. Chem. Soc. Rev. 7, 235—263 (1978); 127 references]

[Rd 38 IE]

The synthesis and chemistry of cyclopropabenzenes is the topic of a comprehensive report by *W. E. Billups*. The parent compound cyclopropabenzene *(2)* is accessible by several routes, *e.g.* from 1,4-cyclohexadiene *(1)*. Mono- and bis(cyclopropa)naphthalenes have also been synthesized. In the presence of Ag^+, compound *(2)* acts as an excellent benzylation reagent. Butadiene and *(2)* undergo thermal addition *via* ring expan-



(1) *(2)*

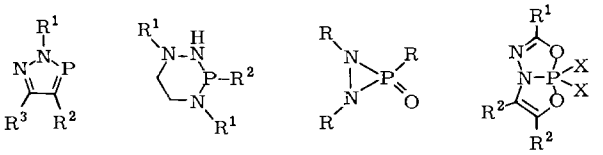
sion to, *e.g.*, 1-vinylindan *(3)*, and Ag^+-catalyzed addition to give *(3)* and pentadienylbenzene. A final decision regarding the extent of double bond localization in *(2)* has yet to be reached. [Synthesis and Chemistry of Benzocyclopropenes. Acc. Chem. Res. *11*, 245—251 (1978); 51 references]

[Rd 36 IE]

The papers presented at the symposium "Chemistry and Flavour" have been collected in a single issue of Chemical Society Reviews. *H. Boelens et al.* report on molecular structure and organoleptic quality, *W. Schlegel* deals with the application of research results to the development of commercial flavors, *K. R. Butterworth* evaluates the safety of natural and synthetic flavors, *W. H. Nightingale* discusses the influence of legislation on flavor chemistry, *J. S. Swan* and *S. M. Burtles* outline the development of flavor in potable spirits, and finally *R. Swindells* deals with the influence of flavor chemistry on consumer acceptence. [Chem. Soc. Rev. 7, 167—218 (1978); total of 87 references]

[Rd 37 IE]

The synthesis and reactions of heterocycles containing a P—N—N linkage are reviewed by *J.-P. Majoral*. The heterocycles are classified according to the number of ligands at the phosphorus atom. Examples of compounds containing di-, tri-, tetra-, and pentacoordinated phosphorus are the heterocycles of type *(1)* to *(4)*. The reactions listed include primarily

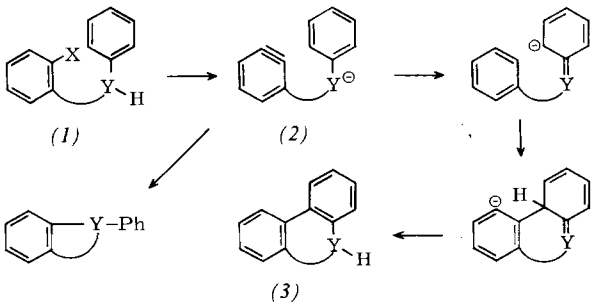


(1) *(2)* *(3)* *(4)*

those in which the coordination number of the phosphorus changes and/or a new heterocycle is formed. [Synthesis and Reactions of Heterocyclic Compounds Containing a P—N—N-Linkage. Synthesis *1978*, 557—576; 89 references]

[Rd 41 IE]

The synthesis of polycyclic systems by intramolecular ring closure *via* a benzyne derivative *(2)* generated *in situ* is the subject of a report by *S. V. Kessar*. The synthetic principle of the reaction is illustrated in the scheme; Y is an atom such as C, P, Si or preferably N, which can carry a negative charge; X is *e.g.* Cl. A detailed study has been carried out on the synthesis of phenanthridine, which is obtained from a dihydro precursor of type *(3)*. [A Novel Route to Condensed Polynuclear Systems; Reality and Illusion of Benzyne Intermediacy. Acc. Chem. Res. *11*, 283—288 (1978); 65 references]



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

[Rd 40 IE]

The lectins have been comprehensively reviewed by *I. J. Goldstein* and *C. E. Hayes*. Lectins are carbohydrate-binding proteins (glycoproteins) which occur in plants and animals; these compounds were previously referred to as *e.g.* agglutinins, hemagglutinins or phytohemagglutinins. An example of the specificity of the lectins is the ability of lima bean extracts to agglutinate exclusively erythrocytes of type A, *i.e.* this lectin can distinguish the blood groups whose determinant groups are carbohydrate chains. The biological function of the lectins is still not absolutely clear. Lectins are used, *e.g.* for blood group determination and for the detection of macromolecules which contain carbohydrates. Membrane-bound carbohydrate-containing structures can be investigated with lectins of defined specificity. [The Lectins: Carbohydrate-binding Proteins of Plants and Animals. Adv. Carbohydr. Chem. Biochem. *35*, 127—340 (1978); 875 references]

[Rd 42 IE]

BOOK REVIEWS

Grundlagen der Technischen Elektrochemie (Fundamentals of industrial Electrochemistry). By *E. Heitz* and *G. Kreysa*. Verlag Chemie GmbH, Weinheim—New York, 1977. 1st edit., xiv, 290 pp., 69 figs., 20 tables, paperback, DM 48.00.

Since electrochemical methods are now gaining ground in many sectors of chemistry, we must welcome this book, which discusses the electrochemical aspects of industrial chemistry.

This is a guide for experimental work. The first chapter deals with experiments involving the most common measuring techniques. The next chapter is devoted to material, charge, and heat transport. Most of the experiments come under the heading of electrochemical reaction technology. The following chapter covers electrode kinetics, kinetics in electrochemical reactors, separation systems in electrochemical cells, optimization and experimental design, problems of structural materials and corrosion, and model experiments concerning the industrial control of reactions. Finally, a long appendix covers electrochemical and industrial fundamentals, calculation exercises and the results and discussion of experiments.

The individual chapters have a logical structure: the authors first mention the most important relevant literature, explain the basic concepts, and give instructions for useful experiments. The latter are particularly well chosen, for they illustrate equally well the fundamentals and the industrial applications. The authors have incorporated their vast practical experience into the presentation of the experiments. We can only agree with their suggestion that one or another experiment should be included in industrial chemistry or physical chemistry practicals. This manual certainly fills a gap and can be recommended to everyone interested in the application of electrochemical methods.

H. Baumgärtel [NB 425 IE]

Grundlagen der Biochemie I and II (Fundamentals of Biochemistry). By *O. Müller*, Georg Thieme Verlag, Stuttgart, 1977. 1st edit., vol. I: Biochemische Reaktionen (Biochemical Reactions), xiii, 393 pp., 58 figs., 40 tables, paperback, DM 24.80. Vol. II: Stoffwechsel der Organismen (Metabolism of Organisms), x, 345 pp., 115 figs., 78 tables, 1 folding table, paperback, DM 24.80.

A new pocketbook on biochemistry has been published, which is planned for three volumes (the last volume, on metabolic regulation, has not yet appeared) each costing almost DM 25.00. The total price is therefore DM 75.00, which in itself invites comparison with the major standard works. It is ambitious, for it is intended—as the preface says in both volumes—"for students of biochemistry and related subjects such as microbiology, botany, zoology, medicine, pharmacy, agriculture, food chemistry, chemistry, and physics, who want to learn the fundamentals of general biochemistry in a short

time. It is also intended as a self-study aid for chemists and biologists in industry and in schools". Such a textbook could hardly be more ambitious, and it must therefore be judged by like standards. The American textbooks, which are much admired with good reason, set about their task with great enthusiasm and gusto and are aimed at a limited audience—yet they give much to many. They present exemplary science in unpretentious colloquial language; they are admittedly not always right by model-school standards, but they are always stimulating, with suggestions, examples and digressions, give us the feeling that something has finally "clicked", and show things in a different light. We find in them with delight and satisfaction all that makes biochemistry such a fascinating subject: its position between two sciences, encompassing the horizons of both chemistry and biology, and a system of adaptable coordinated hierarchies, which was elaborated by the study of evolution and gives us something to ponder over even in the case of non-biological material. But none claims a "didactic concept" based on "remarkable successes", or "comprehensive treatment" ... "based on the systematic discussion of reaction types", behind which the student finds the usual pushbutton approach of chemical cramming schools. Enthusiasts will miss in these volumes (but also in the American textbooks) explicit references to sophisticated metabolic reactions with ylides, hybrid ions, and organometallic compounds, or to one-electron oxidations, transition states with carbonyl groups, and covalent catalysis, to mention but a few. If such examples are found, they come where they are least expected; we find there also suggestions as to how reaction mechanisms can be deduced from kinetic measurements, isotope-exchange reactions, chiral transformations, *etc.*, as well as ideas of what a preparative chemist can learn from biochemical reactions about catalytic tactics and biomimetic strategy. The author also specifies the function of biochemistry as an intellectual exercise-ground and a means for investigating intermolecular interactions and mechanisms of catalysis, but does not mention it as being a rational basis for molecular pharmacology and a challenge to synthetic chemists. On the other hand, we do find a useful classification of enzymatic reactions according to their course and occurrence, and lists and formulas of memory-taxing substances isolated from cells and tissues. However, there is nothing here that we have not heard quite often before; at this above-average price and with its exorbitant claims, this is not a book that is long overdue.

L. Jaenicke [NB 427 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Modified Cellulosics. Edited by *R. M. Rowell* and *R. A. Young*. Academic Press, New York 1978. xii, 361 pp., bound, $ 23.00.—ISBN 0-12-599750-7

Introduction to Stereochemistry. By *K. Mislow*. W. A. Benjamin, Reading 1978. 6th impression. xii, 193 pp., paper, $ 11.50.—ISBN 0-8053-7101-X, pbk.

Intermolecular Forces. By *T. Kihara* and *S. Ichimaru*. John Wiley & Sons, New York 1978. vii, 182 pp., bound, £ 9.50.—ISBN 0-471-99583-5

Die Beständigkeit von Kunststoffen und Gummi. By *B. Dolezel*. Edited and supplemented by *C.-M. von Meysenburg*. Carl Hanser Verlag, München 1978. xii, 684 pp., bound, DM 320.00.—ISBN 3-446-12394-6

Progress in Mass Spectrometry, Vol. 4. Fundamental Aspects of Organic Mass Spectrometry. By *K. Levsen*. Verlag Chemie, Weinheim 1978. xiii, 312 pp., bound, DM 88.00.—ISBN 3-527-25789-6

Grundlagen der Dimensionierung des Gas/Flüssigkeit-Kontaktapparates Bodenkolonne. By *J. Stichlmair*. Verlag Chemie, Weinheim 1978. viii, 187 pp., paper, DM 48.00.—ISBN 3-527-25811-6

Statistische Versuchsplanung. By *G. Retzlaff, G. Rust*, and *J. Waibel*. Verlag Chemie, Weinheim 1978. 2nd revised Edition. xi, 211 pp., bound DM 58.00.—ISBN 3-527-25779-9

Biostatistics: A Foundation for Analysis in the Health Sciences. By *W. W. Daniel*. John Wiley & Sons, London 1978. 2nd Edition. 504 pp., bound, *ca.* £ 12.65.—ISBN 0471-02591-7

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High-Resolution, Higher-Order UV/VIS Derivative Spectrophotometry

New analytical methods (14)

By Gerhard Talsky, Lothar Mayring, and Hans Kreuzer[*]

Dedicated to Professor E. O. Fischer on his 60th Birthday

Derivative spectrophotometry has gained increasing importance in the past two years and is currently experiencing vigorous development. Following an introduction the present article provides a review of this extremely effective method. In particular, the advantages of *higher*-order derivative spectrophotometry (HODS method, $n>2$) are discussed on the basis of practical examples from a wide range of analytical fields. The results are achieved with the aid of a newly developed analog computer unit, whereby for the first time readily reproducible, low-noise, on-line spectra can be obtained up to the 7th order and even, in favorable cases, up to the 9th order. In practice it has proved valuable to work with spectra of the 3rd to 5th order; but even higher derivations could be profitable for the separation of strongly superposed signals or for "fingerprinting".

1. Introduction

After the introduction of derivative spectrophotometry by *Hammond* and *Price*[1], *Tannenbauer et al.*[2], *Morrison*[3], and *Giese* and *French*[4], in the early 50's, the differentiation of experimental curves has been applied to many analytical processes. From the very large number of methods and investigations a representative selection may be made here as follows:

UV/VIS absorption spectrophotometry[2, 5–11]
IR and Raman spectrometry[12–16]
NMR spectrometry[17–19]
ESR spectrometry[18–20]
Flame emission and absorption spectrometry[21–25]
Luminescence spectrometry[26]
Atomic and molecular spectroscopy[27]
Gas chromatography[28, 29]
Polarography[30]
Potentiometric titration and other electroanalytical procedures[31–36]
Investigations of reaction kinetics[5, 37–42].

In the past two years derivative spectrophotometry has acquired increasing importance especially in the field of trace analysis[11, 15, 43–45]. It has also begun to be gradually accepted in UV/VIS spectrophotometry and is now undergoing vigorous development.

Unlike gases and vapors, which frequently give many sharp lines in the UV and in the visible part of the spectrum, dissolved substances or liquids usually give less-characteristic spectra with more or less developed maxima and shoulders, which must be ascribed to the overlapping of several terms of electron transitions, such as $n\rightarrow\pi^*$, $\sigma\rightarrow\sigma^*$, and $\pi\rightarrow\pi^*$, and to rotation and translation.

Derivative spectra make it possible to determine flat maxima more precisely and to isolate shoulders and weak signals from an unwanted background.

The current rapid development of derivative spectrophotometry has mainly been due to progress in modern electronics, which has enabled analog differentiation of the signals to

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be carried out relatively simply in on-line operations; however, to the best of our knowledge only the first- or second-order derivatives of fundamental spectra have hitherto been recorded in this way.

The more expensive digital differentiation increasingly makes use of semiconductor storage and microcomputers in off-line operation.

By means of an electronic analog differentiator newly developed by us[46-48] and capable of wide variation, we have investigated systematically whether, and to what extent, *higher* derivatives, in particular, improve the information obtainable from UV/VIS spectra.

2. Theoretical Principles

2.1. Explanations to the Term "Differentiation"

The differentiation of a curve or of its function means, mathematically expressed, determination of the slope of the curve over the whole region.

In spectrophotometry the ratio of the light flux intensity I_0 before entering the sample to that of the light flux I after leaving the sample is determined. According to the Beer-Lambert law the following relationship is obtained:

$$\frac{I}{I_0} = e^{-cd\varepsilon} \tag{1}$$

(c = concentration of the sample [mol/l], d = layer thickness [cm], ε = molar extinction coefficient).

For a constant intensity I_0 over the whole wavelength range, which is achieved technically *e.g.* by an automatically controlled slit or automatic electronic adjustment of the amplification, the first derivative of Eq. (1) is obtained as:

$$\frac{\frac{dI}{d\lambda}}{I} = -cd\frac{d\varepsilon}{d\lambda} \tag{2}$$

The first derivative is directly proportional to the concentration at each wavelength. The sensitivity of the measurement is particularly high in the neighborhood of inflections, since here there are extremum values of $d\varepsilon/d\lambda$.

For the second derivative we find:

$$\frac{\frac{d^2I}{d\lambda^2}}{I} = c^2d^2\left(\frac{d\varepsilon}{d\lambda}\right)^2 - cd\frac{d^2\varepsilon}{d\lambda^2} \tag{3}$$

Direct (linear) proportionality to the concentration then exists only if the first derivative of ε (*i.e.* $d\varepsilon/d\lambda$) is equal to zero. If, additionally, $d^2\varepsilon/d\lambda^2$ (the second derivative of ε) has an extremum value, then the sensitivity is particularly high.

Likewise, for the third derivative:

$$\frac{\frac{d^3I}{d\lambda^3}}{I} = -cd\frac{d^3\varepsilon}{d\lambda^3} + 3c^2d^2\frac{d\varepsilon}{d\lambda}\frac{d^2\varepsilon}{d\lambda^2} + c^3d^3\left(\frac{d\varepsilon}{d\lambda}\right)^3 \tag{4}$$

$d\varepsilon/d\lambda$ must be zero if it is to be linearly proportional to the concentration. Particularly high measurement sensitivity is obtained at shoulders with horizontal tangents to the points of inflection and small radii of curvature.

If, however, the first derivative is not zero, *i.e.* if one is dealing with points not having horizontal tangents, then special nonlinear calibration curves must be prepared.

Equations for still higher derivatives can be set up in similar fashion. For the fourth derivative it should be noted that linear proportionality is achieved only when both $d\varepsilon/d\lambda$ and $d^2\varepsilon/d\lambda^2$ assume values of zero.

$$\frac{\frac{d^4I}{d\lambda^4}}{I} = -cd\frac{d^4\varepsilon}{d\lambda^4} + 4c^2d^2\frac{d\varepsilon}{d\lambda}\frac{d^3\varepsilon}{d\lambda^3} + 3c^2d^2\left(\frac{d^2\varepsilon}{d\lambda^2}\right)^2 - c^4d^4\left(\frac{d\varepsilon}{d\lambda}\right)^4 \tag{5}$$

2.2. Derivations of Analytical Bands

An absorption band, also called an analytical band, can be described by approximation formulas such as the Gauss and Lorentz functions or the Cauchy distribution. According to *Gauss*, the extinction E of the band at wavelength λ is given by:

$$E_\lambda = E_{max}\, e^{-C\lambda^2} \tag{6}$$

(E_{max} = extinction of the absorption maximum, C = const)

and for the half-width s, by which is meant the distance, parallel to the abscissa, between the points of inflection of the curve, we have:

$$s = \sqrt{\frac{2}{C}} \tag{7}$$

The differentiation of a simple analytical band is represented graphically in Figure 1a. The maximum of the fundamental curve in derivatives of odd order corresponds to a passage through zero, and in even-order derivatives it corresponds to an extremum value (alternately minimum and maximum). With increasing order of the derivative the sharpness of the bands increases, while the band width decreases. Inflections on the fundamental curve lead to extrema in the derivatives of odd order and to passages through zero in derivatives of even order, which explains the increase in the number of extrema over that on the fundamental curve. One speaks here of "virtual extrema", since they do not occur on the fundamental curve but are formed from the inflections on differentiation. The result is that the inflections are more readily determined and the spectrum is therefore easier to resolve and, on the other hand, with increasing order simplicity is lost because of the increase in the number of extrema—one maximum produces $n+1$ extrema in the nth derivative.

The advantage of derivative spectrophotometry is thus especially evident on the examination of curves that arise by the overlapping of two or more analytical bands (Gaussian curves):

$$E_{(\lambda)} = E_{1(\lambda_0)} + E_{2(\lambda_0 - \Delta\lambda)} \tag{8}$$

($E_{(\lambda)}$ = superposition, $E_{1(\lambda_0)}$ = absorption bands with maximum at λ_0, $E_{2(\lambda_0-\Delta\lambda)}$ absorption bands whose maximum is shifted from $E_{1(\lambda_0)}$ by $\Delta\lambda$).

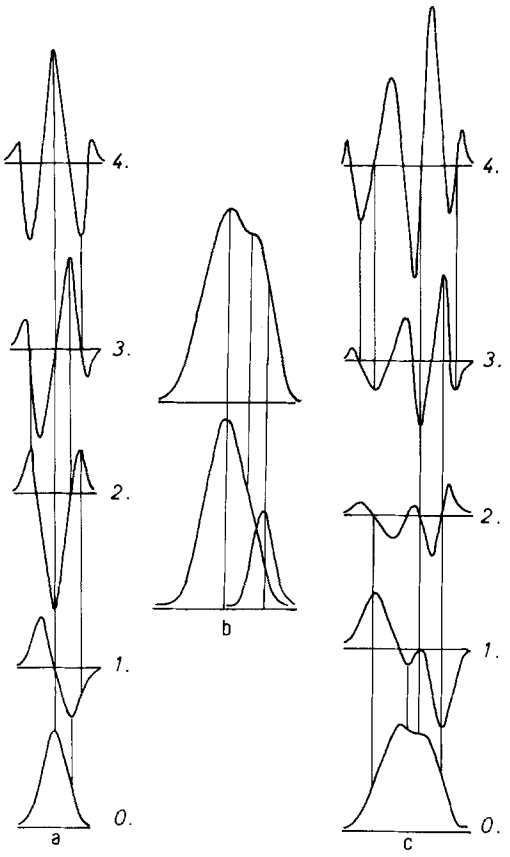


Fig. 1. a) Differentiation of a Gaussian curve (analytical band); fundamental curve and 1st to 4th derivative [$E_\lambda = E_0 \exp(-C\lambda^2)$]; b) superposition of two unequal Gaussian curves [$E_\lambda = E_{1(\lambda_0)} + E_{2(\lambda_0 - \Delta\lambda)}$]; c) Differentiation of two superposed unequal Gaussian curves; fundamental curve and 1st to 4th derivatives.

In cases where there is superposition of two equal Gaussian curves, a third or fourth inflection arises if $\Delta\lambda$ corresponds to at least the half-width.

If, however, bands with *different* ordinates of their maxima overlap, then shoulders are formed even if the separation of the maxima is less than the largest half-width; on further separation of the bands the shoulders are converted into terrace points, this feature being connected with the appearance of a fourth inflection on superposition (Fig. 1b).

If this fundamental curve is differentiated, then in the odd derivatives the terrace point becomes an extremum value (*e.g.* in the third derivative the most intense minimum), whereby a better resolution of the spectrum and also a quantitative determination of both components become possible (Fig. 1c).

2.3. Loss of Information on Differentiation—Increase in Resolution

Any function can be represented approximately by a power series, for example:

$$E_\lambda = c_0 + c_1\lambda + c_2\lambda^2 + c_3\lambda^3 + U_\lambda \tag{9}$$

If this equation is differentiated, the constant c_0 vanishes and the linear term $c_1\lambda$ becomes a constant:

$$E'_\lambda = c_1 + 2c_2\lambda + 3c_3\lambda^2 + U'_\lambda \tag{10}$$

In practice this means that a linear background can be eliminated (Fig. 2).

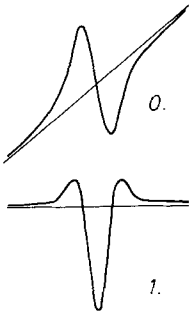


Fig. 2. Elimination of a linear background function ($y = ax$) by differentiation (1st derivative, $dE/d\lambda$).

On the second differentiation of the fundamental function (9)

$$E''_\lambda = 2c_2 + 6c_3\lambda + U''_\lambda \tag{11}$$

the terms $c_0 + c_1\lambda$ vanish, since they become constants, and $c_2\lambda^2$ (*i.e.* a parabolic background function) is converted into a linear function.

Derivatives of higher order also eliminate background functions of higher order and complicated shape:

$$E'''_\lambda = 6c_3 + U'''_\lambda \tag{12}$$

$$E''''_\lambda = \quad U''''_\lambda \tag{13}$$

Resolution is thus improved by the sharpening of signals that is achieved by derivative spectrophotometry. In the case of Lorentzian or Gaussian functions the ratio of the half-width of the primary function to the half-width of the 2nd derivative is 1:0.33, *i.e.* it decreases to a third of its original value. However, if special measures are not taken, noise increases by a factor of $0.33^2/1$, *i.e.* becomes 10 times greater[49]. A derivative order greater than $2n$ ($n = 1, 2, \ldots$) is generally used, since in this case the extremum values correspond to one another[50] (Figs. 3a and 3b).

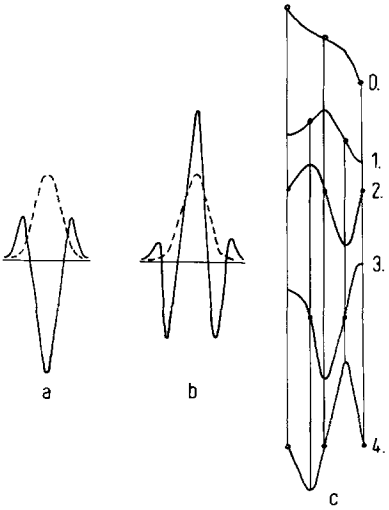


Fig. 3. Sharpening of signals by differentiation of the maxima. a) Fundamental function (---) and the 2nd derivative $d^2E/d\lambda^2$ (—); b) fundamental function (---) and the 4th derivative of $d^4E/d\lambda^4$ (—); c) signal sharpening by differentiation of shoulders; fundamental curve and the 1st to 4th derivatives.

Extreme sharpening of signals can also be observed when shoulders are resolved. Two effects are then produced (Fig. 3c):

a) Conversion of a shoulder into an extremum value in the derivatives of odd order,

b) the signal sharpening shown in Figures 3a and 3b.

Band overlaps may be resolved by a) and the fine structure of the spectra is emphasized by b), which is important for identity and purity tests (fingerprint spectra, see for example Fig. 18). In analysis, and particularly in biochemical analysis, this procedure is in many cases superior to the customary formation of the ratio of absorptions at two wavelengths as a criterion of purity (*e.g.*[11]). In the higher derivatives, however, the spectra become increasingly complex, which can make their evaluation more difficult.

Derivative spectrophotometry cannot increase the amount of information in the spectra—this is determined by the standard of the spectrophotometer—but it can increase the resolution at the cost of loss of the background signals, and can thus considerably improve the detection sensitivity of masked weaker bands or it can even make possible for the first time a qualitative or quantitative determination of these bands.

Further works on the theory of derivative spectrophotometry can be found in [51–60].

2.4. Evaluation of Derivative Spectra for Quantitative Measurements

As stated in Section 2.1, there are certain conditions in which the derivatives of I/I_0 are linearly proportional to the concentration and need not first be converted into extinctions by means of logarithms.

In the *tangent method* a common tangent is drawn to two neighboring maxima or minima and the distance t to the intermediate extremum value is measured parallel to the ordinate (Fig. 4). This method can be applied satisfactorily with a linear background.

The distance p between two extremum values is proportional to the difference between the slopes of the tangents to the inflections on the fundamental curve. This is called the *peak-peak* method and is most often used for quantitative multicomponent analyses. Two examples—p_1 and p_2—are illustrated in Figure 4.

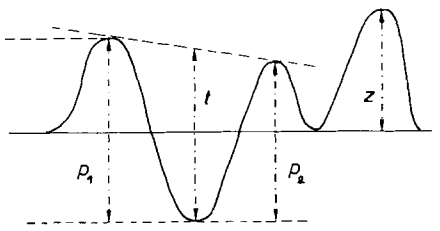


Fig. 4. Evaluation of derivative spectra. Tangent method (t), peak-peak method (p), and peak-zero method (z) (see Text).

The *zero-crossing method (peak-zero method)* is used only in special cases. In this the vertical distance z to the zero line is measured (Fig. 4); the method is suitable for the evaluation of higher derivatives containing signals symmetrical with respect to the abscissa and in cases of undistorted overlapping of individual curves if one of the curves passes through zero at this position.

Finally the ratios between pairs of neighboring peaks ($p_1 : p_2$) can be determined; if these differ, then background interference and, therefore, inferior quality of the sample are indicated (*peak-peak ratio method*) (Fig. 4).

3. Experimental Verification of Derivative Spectra

3.1. Electromechanical Tachometer

Olson and *Alway*[61] have described a method of recording the first derivative. The authors used a recorder with a tachometer generator and a lock-in amplifier followed by a filter. On wavelength scanning the rate of movement of the recorder in the ordinate direction is proportional to the first derivative.

Klein and *Dratz*[62] and *Cook*[63] produced, by a tachometer generator, a 60 Hz signal whose amplitude was proportional to the ordinate component; after amplification by a lock-in amplifier it was rectified, smoothed, and filtered.

3.2. Modulation Processes

In sinusoidal wavelength modulation the main wavelength λ_0 is sinusoidally modulated:

$$\lambda - \lambda_0 = d \cdot \sin \omega t \qquad (14)$$

(λ = auxiliary wavelength, d = vibration range, ω = angular velocity, t = time).

This is achieved *e.g.* by vibrating lattices, quartz plates, mirrors, vibrating exit slits, or optical wobblers[52, 55, 64–68]. Modulation of the wavelength induces a synchronous modulation of the amplitude. If these intensities are expanded in the form of a Taylor series in λ_0 and the powers of the sine functions are expressed as sine and cosine functions of the corresponding multiple angles, then the derivatives can be obtained from the Fourier coefficients of this series. The second derivative is obtained from the second harmonic of the induced intensity. *Hager* and *Anderson*[55] give a complete theoretical description of the sinusoidally modulated derivative spectrometer. The second possibility, namely direct modulation of the amplitude, is used only rarely.

3.3. Two-wavelength Spectrophotometry

This method of differentiation, also an optical one, which dates back to *French*'s investigations[69], was developed further and used by *Saidel*[70] and, especially by *Shibata*[7, 71].

In this method the light is divided between two monochromators and its intensity is measured by two identical photomultipliers. The signals are then directed, after amplification, to a subtraction unit whose output is connected to the Y-input of a recorder; the X-axis of the recorder is driven synchronously with the wavelength scan. If the difference between the wavelength scans is sufficiently small (usually 1–2 nm), the first derivative with respect to the wavelength is obtained. The time constant can be adjusted by altering the wavelength difference (time interval of the scan) of the monochromator. Higher derivatives cannot be obtained directly by this method.

3.4. Derivative Spectrophotometry by Subtraction of Temporally or Spatially Delayed Spectra

Another instrumental arrangement for obtaining the first derivative has been described by *Grum et al.*[72]. The output of the photomultiplier is divided into two equal parts. One signal passes direct to the subtraction unit, the other signal is first delayed in time or space by an electronic or electron-optical circuit.

The output signal from the subtraction unit is passed to the recorder and is directly proportional to the first derivative of the spectrum.

Inoue et al.[73] have developed a technique in which the signal delay is produced by tape recording with two recording heads arranged in tandem. The time constant is given, and can be regulated, by the separation between the recording heads.

Apparatus for the temporal or spatial delay to the spectra described here is relatively easily constructed for the first derivative and affords a differentiation with respect to time. Higher derivatives have not so far been obtained in this way; the cost of this would be relatively high.

3.5. Digital Differentiation

One method requiring expensive apparatus makes use of a numerical calculation of the derivatives by digital computer[74, 75]. The calculation can be effected on-line or off-line[72]. The output signal of the spectrophotometer must first be fed to an analog-digital converter. To increase reproducibility, the signals at each given wavelength are accumulated and smoothed out; the mean value is then calculated (off-line). In other procedures the curves are smoothed by the method of least squares. The differentiation can also be programmed point by point or by the use of Lagrange differentiation polynomials. The wavelength separation in the measurement is usually 0.1–1.0 nm. The spectrum and its derivatives can be interpolated by linear regression.

For the analysis of digitalized spectra *Morrey*[76] used a large computer. To determine the positions of the absorption bands, the second, third, and fourth derivatives were calculated, and from them the signal width and the relative amounts of the components could be obtained.

Butler and *Hopkins*[77–79] investigated pigments in suspensions of mitochondria, chloroplasts, and yeast cells. The background function due to scattered light and other components was eliminated by electronic function simulation or off-line, after digitalization and storage, by pointwise digital differentiation. These authors also carried out empirical computer analyses of the spectra and give examples of derivative spectra of second and fourth orders.

In the past months less expensive and less complicated digital differentiators, generally based on microcomputers, have come onto the market. Hitherto they have usually been designed for giving only the first and second derivatives and provide few possibilities of variation. Recently also, MC differentiators have been offered for derivatives up to the fourth order; there have been no accounts of experience with these modules in the literature, apart from intrafactory reports. As long as the microcomputer has sufficient storage capacity one can in fact carry out differentiations of any desired order by retrieving the fundamental spectrum from storage, differentiating it, storing that result, differentiating this in its turn, and repeating this process n times. However, with increasing order the errors in the approximate solutions become increasingly evident, being shown by slightly jagged curves and an increasing noise level.

3.6. Electronic Analog Differentiation

Analog differentiation by means of electronic differentiation circuits presents a series of advantages over the methods described in Sections 3.1 to 3.5:

- Modification of the optical system is omitted.
- The use of lock-in amplifiers is avoided.
- Feedback on the measuring process is easy to avoid.
- All the advantages of analog data processing (*e.g.* filtering, smoothing) are retained.
- Time constants, filters, attenuation, *etc.* can be easily optimized.
- Higher derivatives can be obtained relatively simply.
- Susceptibility to disturbance is small.
- Costs are relatively low; the cost/performance ratio is good.

Against these advantages must be set some disadvantages:

- The differentiation is not carried out directly with respect to wavelength, but with respect to time. This, however, does not interfere if the wavelength scan is effected at a constant rate.
- The derivative spectra are somewhat delayed with respect to the fundamental spectrum, this being caused by the RC units. This phase shift depends on the differentiation time constant and on the rate of the wavelength scan. The shift of the signals can be taken into account by standardization or calculation[80] (systematic error). A further possibility is to compare the derivative spectra by scanning the fundamental spectrum in the forward and reverse directions, followed by formation of the mean.
- Reproducible and time-constant wavelength scanning is absolutely essential (*e.g.* synchronous operation of wavelength scan and recorder travel by stepping motors or other devices). This can be effected easily with lattice monochromators or—but only with great difficulty—with prism instruments having logarithmic scales.
- The bandwidth of the light must be independent of λ; the method is thus unsuitable for spectrophotometers with automatically adjusted slits.

For derivative luminescence spectrophotometry, *Green* and *O'Haver*[26] have been able to show that the wavelength-modulation technique and electronic analog differentiation give the same signal/noise ratio and that there is no difference for other spectral parameters either[81–83].

4. Electronic On-line Analog Differentiation of Higher Order

Electronic analog differentiation can be achieved in the simplest case by a combination of a condenser C_s and a resistance R_r. This passive constructional unit is preferably

connected to an operation amplifier OP (Fig. 5). The operation amplifier should here be regarded as a "black box". On an

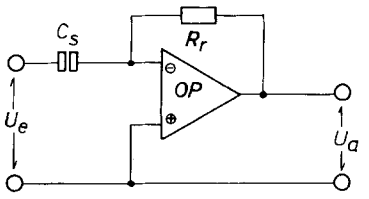


Fig. 5. Basic circuit of an inverting differentiator (U_e input potential, U_a output potential, C_s condenser, R_r feedback resistance, OP operation amplifier).

area of 1—2 m^2 this modern integrated active element takes over the functions of eight to ten transistors and of several resistances and condensers and amplifies the signal after input in equipolar fashion (⊕), *i.e.* with the same sign, or inverted (⊖) (no-load amplification 1000—100000!). The differentiation time constant τ is obtained from:

$$\tau = C_s \cdot R_r \tag{15}$$

and it can thus be adjusted by varying the capacitive component or the ohmic component.

The resolution of the derivative spectrum depends not only on the slit width but also to a large extent on the rate of the wavelength scan S and on τ. The best resolution is thus obtained with a small slit width, slow scan, and small τ. In practice a middle way must be chosen, because if the slit is narrow the noise increases greatly owing to the high amplification and gives a poor zero-line constant, which has a detrimental effect on the reproducibility of the derived spectra. If both S and τ are small, then again only small differences in potential are obtained, as we have:

$$\frac{dE}{d\lambda} \sim \frac{dE}{dt} \sim \frac{dU}{dt} \tag{16}$$

In optimizing the differentiator care must be taken that the resolution A_D of the differentiator is at the most equal to—but is better smaller than—the spectral bandwidth, since otherwise valuable information is lost and the resolution of the spectra becomes worse. On the other hand, in special cases this particular effect can be made useful—to damp down or suppress disturbing signals in the spectrum. The time resolution T of an analytical band amounts, for the first derivative to:

$$T_1 \sim 4\tau_1 = 4RC \text{ [s]} \tag{17}$$

and for the second derivative to:

$$T_2 \sim 8\tau_2 = 8RC \text{ [s]} \tag{18}$$

This gives the resolution of the differentiator:

$$A_D = T \cdot S \text{ [nm]} \tag{19}$$

(S = scan [nm/s])

When the spectral bandwidth B of the apparatus has been adjusted we should have:

$$A_D \leqq B \tag{20}$$

and

$$T < \frac{B}{S} \tag{21}$$

Except in cases of extreme difficulty, spectral bandwidths of 0.5—2 nm, a wavelength scan rate S of 1—5 nm/s, and differentiation time constants τ between 0.1 and 1 s are usually chosen.

While with the fundamental circuit the first or, in the most favorable case, the second derivative is obtained, with higher derivatives the noise becomes so great that the reproducibility—the prerequisite for quantitative evaluation—becomes very unsatisfactory.

By "noise" is understood the, generally higher-frequency, variation of the signal potential around a central value. The following are the principal causes:

a) Noise from the sample, *e.g.* due to temperature gradients, inhomogeneities or scattering.
b) Noise from the optics due to fluctuations of the light source.
c) Noise from the electronics of the spectrophotometer, mostly from the multiplier and amplifiers.
d) Noise from the differentiator unit, mainly the intensification of noise by differentiation.

Since the output voltage of a differentiator is directly proportional to the change in the input voltage with time, the (higher-frequency) noise is amplified in preference to (lower-frequency) signal voltage. The noise level therefore increases exponentially with the order of the derivative. Consequently, in derivative spectrophotometry spectral resolution and noise suppression are two opposing effects, which must be optimized from case to case.

Hitherto it has been possible to obtain only first- and second-order derivative spectra on-line by analog differentiation. We have now developed an instrument for producing higher-order derivative spectra to test how far the resolution of experimental signals is improved by the higher derivatives and up to which order differentiation still remains useful.

The apparatus consists of nine differentiation modules (inverting and noninverting; tandem differentiators); in addition, there are operation amplifiers, impedance transformers, attenuating units, active and passive filters, measuring devices, and potential dividers for matching input and output (cf. also Fig. 7).

The wide variability of the input source resistance, the input time unit, the amplifiers, the ohmic and capacitive members of the differentiators and filters, as well as of the attenuating units enables the instrument to be adjusted optimally for any desired purpose. Experience gained so far has enabled the important principles for such an electronic circuit to be deduced; in addition, a ratio between efficiency in signal resolution and the expenditure involved has been reached that is favorable for practical use.

What basic demands must an analog differentiator satisfy in order to be useful especially for verifying higher derivatives?

In the first place, care must be taken that the input signals are not affected by the differentiator units and that these units do not affect each other. This is done by placing before and between them impedance transformers with a high input and a low output resistance (galvanic separation). The signal is then raised to 5—10 V by means of a linear operation amplifier of, usually, 10 mV to 1 V peak voltage, this having a beneficial effect on the quality of the subsequent differentiation (short dead time). Both inverting and noninverting modules, the time constants of which should be separately variable, are suitable as differentiators. The noise, which has a decisive effect on the quality of the derivatives, especially those of higher order, can be eliminated by several measures:

a) Damping of the differentiator. This can be brought about for example by placing an ohmic resistance in front of the differentiating condenser or by switchable condensers in the feedback (capacity countercoupling).
b) Repeated differentiation with a large time constant τ. If differentiation is performed with large time constants, the signals with small amplitude and frequency are only poorly resolved in the form of small shoulders in the first derivative but, on further—if necessary repeated —differentiation they are transformed into relative extrema. A spectrum is finally obtained that shows no more shoulders and contains little noise. A disadvantage may be the size of the phase shift, which is proportional to the values of τ and the increase in "virtual" derivative bands caused by the higher order of differentiation.
c) Use of electronic filters. The noise can also be eliminated by the pre- or post-inclusion of passive or active (with amplification) selective electronic filters. A "low-pass" permits all signals to pass almost unhindered up to an adjustable limiting frequency, while the unwanted higher- and high-frequency signals are diverted.—A further possibility consists in the integration of the frequency filter in the feedback of the differentiating unit itself, whereby, for example, the low-frequency signals of interest are differentiated preferentially.—Selective frequency filtration is thus an efficient method for noise suppression, particularly when the limiting frequency and the quality of the filter can be varied separately.
d) Elimination of noise by statistics. This procedure is used above all when only small amounts of the sample are available, when the substances have low extinction coefficients, and/or if, owing to the high amplification, a poor signal/noise ratio is obtained in spite of all the measures described above.—The spectrum is drawn by a recorder with a medium intensity of color, at least ten times in exactly the same place. The regions of high line-density appear more intense and can now either be traced manually or photographed with underexposure on film material having a steep gamma. After copying onto hard paper, areas of high line-density stand out predominantly.—Naturally the superimposed curves could be prepared after digitalization by statistical methods, but this would be much more expensive.

How the individual adaptation of the differentiating units to each particular problem already affects the second derivative is shown in Figure 6. In the spectrum of trypsin, for example,

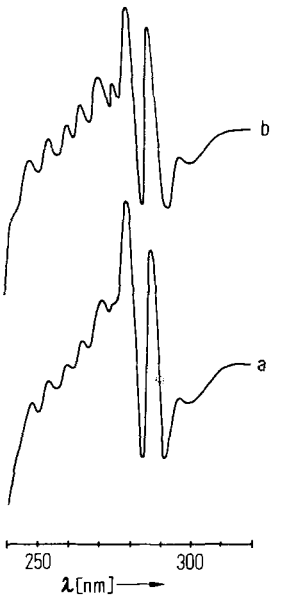


Fig. 6. Comparison of the spectral resolution (bovine trypsin): a) 2nd derivative, obtained by the use of a commercial analog differentiator; concn. 1 g/l, LTH (layer thickness) 1 cm, slit 1 nm, scan rate 1 nm/s, mode 6; b) 2nd derivative, recorded by means of an analog differentiator developed by us; concn. 1 g/l, LTH 1 cm, slit 1 nm, scan rate 1 nm/s.

the weak shoulders at 245 and 275 nm are, in particular, more clearly resolved.

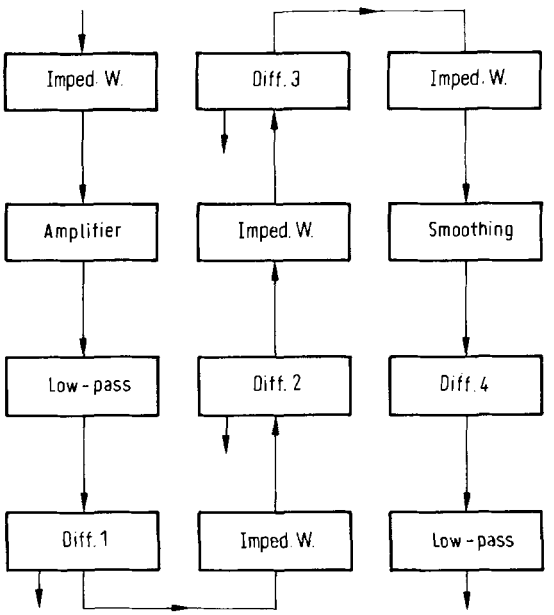


Fig. 7. Block diagram of a differentiator for derivatives up to 4th order.

Finally, it is possible to show by means of a block diagram the preferred construction of a differentiator circuit, in this case for obtaining derivatives up to the fourth order (Fig. 7).

5. Applications of UV/VIS Derivative Spectrophotometry

The following practical examples from the various fields of analysis are designed to demonstrate the wide area of

application of derivative spectrophotometry and, in particular, the capabilities and advantages of *higher*-order derivative spectrophotometry (HODS method; $n > 2$).

specimen. The order chosen should, however, be at least one at which all the shoulders and terraces are converted into bipolar signals. This can usually be attached with the fourth

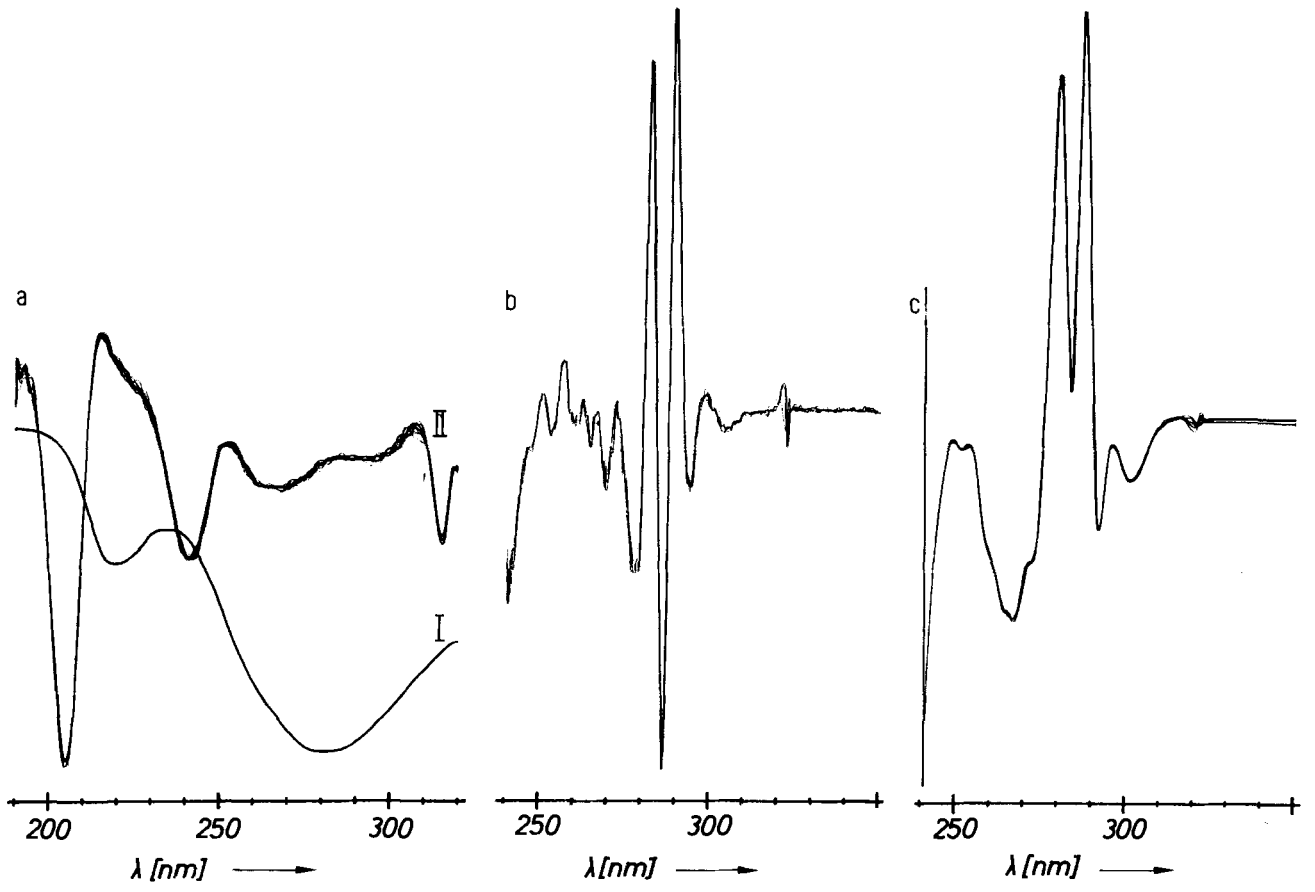


Fig. 8. a) Congo Red, concn. 20 mg/l, LTH 1 cm, slit 1 nm, scan 5 nm/s. I: fundamental spectrum; range 2E; II: 4th derivative, tenfold recording; b) bovine trypsin, concn. 0.5 g/l, LTH 1 cm, slit 1 nm; 4th derivative, sixfold recording, scan 2 nm/s; c) as b), scan 5 nm/s.

Some introductory remarks may first be made about analog differentiation. Figure 8a reproduces an original fourth-order spectrum of the azo-dye Congo Red. The tenfold superposition of recordings of the fourth derivative demonstrates the excellent reproducibility and low noise level; these were achieved by stepwise special adaptation of the apparatus to the problem at hand. The derivatives of spectra with broad maxima and flat flanks can be produced relatively rapidly (scan S about 5 nm/s). With steep and narrow maxima this would lead to reduced resolution, particularly if a large time constant were selected ($\tau \geqq 1$ s); this is shown in Figures 8b and 8c. In Figure 8b a scan of 2 nm/s was chosen. The fine structure of the fourth derivative (trypsin, sixfold superposition) can be well reproduced. However, little of the fine structure is visible in Figure 8c; with a scan rate of 5 nm/s the characteristic bands between 250 and 280 nm are suppressed. A smaller time constant could of course have been chosen, but this is possible only to a limited extent since $dE/d\lambda$ then becomes small, especially in the case of a gentle slope, and the high amplification then necessary increases the noise.

Up to what order is it reasonable to differentiate the fundamental spectrum? This question cannot be answered precisely, because the most favorable order varies from specimen to

or fifth derivative. Still higher derivatives can bring advantages particularly as "fingerprints". Figure 9 shows this for the fundamental spectrum and for the first- to seventh-order derivative spectra of the enzyme ribonuclease A. The fundamental spectrum shows the maximum at about 280 nm that is typical of proteins and a minimum at about 250 nm; shoulders on the flanks are merely hinted at. In the second and third derivatives the fine structure already appears distinctly, and in the fourth derivative it is largely converted into bipolar signals. The fifth to seventh derivatives increasingly sharpen the small maxima. The advantages of higher-order differentiation are increasingly recognizable if in each case the even- and odd-numbered orders are compared with one another. The seventh derivative was recorded 10 times in superposition to demonstrate the excellent reproducibility still shown at such high orders.

While extrema of the fundamental curve are most easily recognized in even-numbered derivatives (see Section 2.2), the inflections are most advantageously resolved in odd-numbered derivatives. It is thus useful to produce spectra of $(2n+1)$-th and $2n$-th order ($n = 0, 1, 2, \ldots$).

In the optimization of the individual steps care must be taken not to exceed the maximal working voltage of the

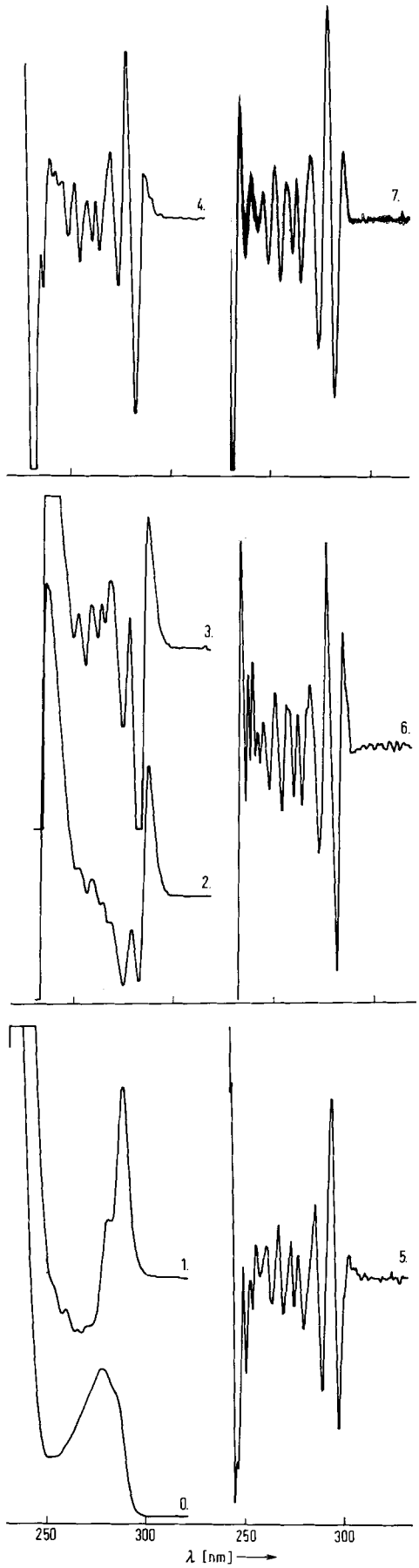


Fig. 9. Ribonuclease A (bovine), concn. 1 g/l, LTH 1 cm, slit 1 nm, scan rate 2 nm/s, range 2*E*; fundamental spectrum and 1st to 7th derivatives. The 7th derivative was recorded tenfold.

IC's used, as otherwise distortion of the spectra and oscillating in the circuit can occur, causing poor reproducibility and severe departure from linearity. When the spectra show flat maxima and poorly developed shoulders it has proved valuable to raise the signal voltage to *ca.* 5—8 V before differentiation. The output from the first stage, which then exhibits a voltage of 10—12 V, is subsequently attenuated to 5—8 V after filtration and is fed to the second stage (differentiation at the same voltage level). If, however, the extrema have steep flanks it is better to raise the input signal only to about 2 V before differentiation; in this case the inputs of the second, third, fourth, and higher stages are raised to 4, 6, 8 V and above (differentiation with rising voltage level).

5.1. Trace Analysis

Purity tests of crude, intermediate, and end products, and the detection of small amounts of impurities in foods, pharmaceuticals, effluents, *etc.* are the subject of much applied analysis. A few examples will be given here.

Ethanol is usually made absolute by ternary rectification with benzene, toluene, or xylene as entraining agents. However, when it is used as raw material for the production of alcoholic drinks, pharmaceutical preparations, extracts, *etc.* no more than traces of such toxic arenes may be present. In the fundamental spectrum of ethanol (layer 1 cm thick) 50 ppm of benzene can just still be determined (±10 %); 10 ppm gives only slight waves (Fig. 10, curve III), and 1 ppm can no longer be detected at all (Fig. 10, curve II). If, however, the spectrum is differentiated several times, the lower detection limit decreases: for the second derivative it is 5 ppm and for the fourth derivative it is reduced at least to 1 ppm (Fig. 10, curve V; mean error of the mean ±5 %), and semiquantitative analysis is still possible even with 100 ppb!

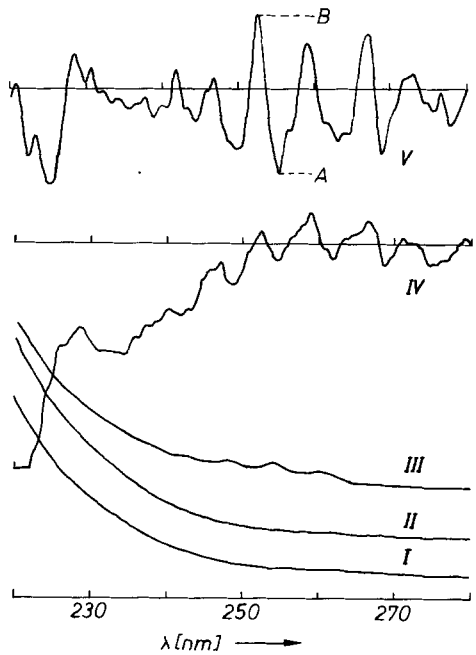


Fig. 10. Quantitative determination of traces of benzene in ethanol. Range 1*E*. LTH 1 cm, slit 1 nm. I: fundamental spectrum of "Uvasol" ethanol; II: fundamental spectrum with 1 ppm of benzene; III: fundamental spectrum with 10 ppm of benzene; IV: 2nd derivative of II (1 ppm of benzene), scan 2 nm/s; V: 4th derivative of II (1 ppm of benzene) scan rate 2 nm/s; $\overline{AB}$ is proportional to the concentration of benzene.

Arenes can similarly be detected in waste gases or waste air. The gases and vapors are drawn through an absorbent liquid such as ethanol, hexane, or cyclohexane and these are then investigated. Alternatively, the procedure described in Section 5.10 for "gases and vapors" is used.

Aniline and phenol are often present in effluents. These compounds can be analyzed very rapidly and simply by derivative spectrophotometry and, if necessary, determined quantitatively and even continuously down to low concentrations (2—5 ppm). Even varying amounts of turbid or colored materials do not usually disturb this analysis, since the background can be eliminated by differentiation.

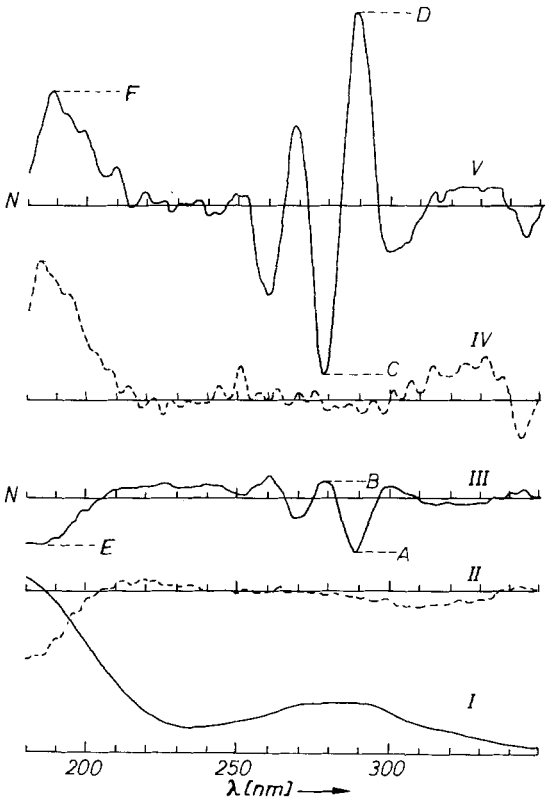


Fig. 11. Quantitative simultaneous determination of aniline and phenol in waste water. LTH 1 cm, slit 1 nm, scan rate 2 nm/s (cf. H_2O). I: fundamental spectrum with 5 ppm contents of aniline and phenol; II: 3rd derivative, 6 ppm of aniline; III: 3rd derivative, 5 ppm contents of aniline ($\overline{EN}$; N = zero line) and phenol ($\overline{AB}$); IV: 4th derivative, 6 ppm of aniline; V: 4th derivative, 5 ppm contents of aniline ($\overline{FN}$) and phenol ($\overline{CD}$).

Figure 11, curve III, shows the third derivative of the spectrum of a mixture of the two substances in a ratio of 1:1 (5 ppm of each) in water. However, they can be determined much more sensitively and simply by means of the fourth derivative (curve V): for instance, 2 ppm of phenol can still be determined with $\pm 5\,\%$ accuracy.

The use of a spectrophotometer with a built-in timer enables effluents to be monitored at predetermined time intervals. A flow-through cell is fed with the effluent *via* a by-pass by means of a peristaltic pump, and the amounts of toxic impurities are determined from the appropriate peak-peak distances in the third or fourth derivatives of the spectra.

Murexide and dithizone are reagents much used in trace analysis for the detection of metal ions; the detection limit lies at 10 to 100 ppm. By higher-order derivative spectrophotometry the sensitivity can be raised by at least one power of ten. The method can also be used with success for other color reactions.

5.2. Dyes

Derivative spectrophotometry can be applied advantageously to tests for identity and purity and to simultaneous quantitative determination of dye mixtures which are important in the manufacture of *e.g.* writing and printing inks and textile dyes, and also of diagnostic agents, pharmaceuticals, cosmetics, and foodstuffs. Of this group we have successfully investigated Congo Red/Cresol Red, Methyl Orange/Acridine Yellow, Rhodamine B, Trypaflavine, Methylene Blue, Brilliant Green, and Quinosol. The third to fifth derivatives were used.

5.3. Isomeric Compounds and Homologous Series

The following systems have been analyzed by HODS:

a) *n*-Propanol/isopropanol (undiluted, fourth derivative).
b) *n*-Butanol/isobutanol (undiluted, fourth derivative).
c) *o*-Xylene/*p*-xylene (1 % in hexane). The fundamental spectra provide little information. However, the *o*- and *p*-compounds can be satisfactorily distinguished in the third-derivative spectrum and can also be determined quantitatively with $\pm 4\,\%$ accuracy in the presence of one another.
d) Methyl, ethyl, and isoamyl acetates (undiluted and in the vapor state, third and fourth derivatives).
e) Benzene in "normal" and "super" gasoline (0.1 % in hexane). The addition of benzene, which increases the octane number, has acquired particular importance from the legal requirement to reduce the lead content of fuels. By means of the third-derivative spectrum (Fig. 12) the benzene contents of "normal" and of "super" gasoline were found to be $2.8 \pm 0.3\,\%$ and $9.8 \pm 0.3\,\%$, respectively, in good agreement with the supplier's specification (2.5—3.5 % and 9.5 to 10.5 %, respectively).

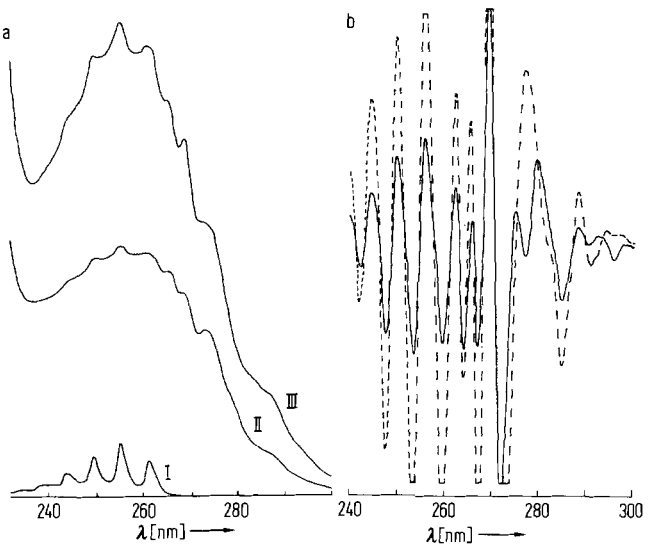


Fig. 12. Benzene in gasoline LTH 1 cm, slit 1 nm, scan rate 2 nm/s (cf. hexane). a) Fundamental spectra; I: 100 ppm of benzene in hexane; II: normal gasoline (0.1 % in hexane); III: super gasoline (0.1 % in hexane); b) 3rd derivatives of II (—) and III (---).

5.4. Foods and Beverages

Derivative spectrophotometry makes it possible, for example, to determine saccharin simply and quantitatively

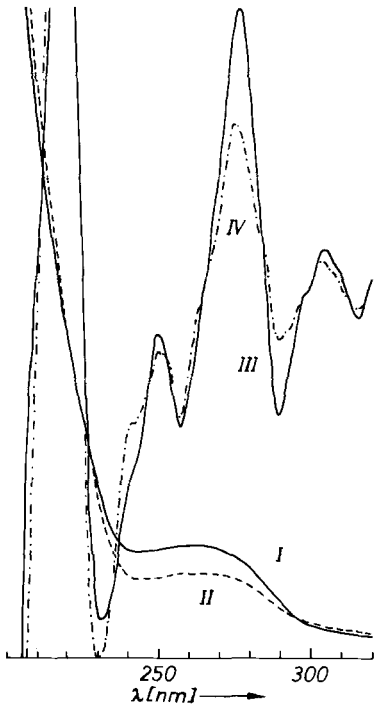


Fig. 13. Characterization of types of beer (0.4% in H_2O, range 2*E*). I: fundamental spectrum of light "Vollbier"; II: fundamental spectrum of "Weizenbier"; III: 4th derivative of I; IV: 4th derivative of II; slit 1 nm, scan rate 5 nm/s, LTH 1 cm.

in fruit juices. By a suitable setting of the differentiator the background due to the slightly turbid fruit juice can be emphasized and then filtered out, yielding the undistorted derivative

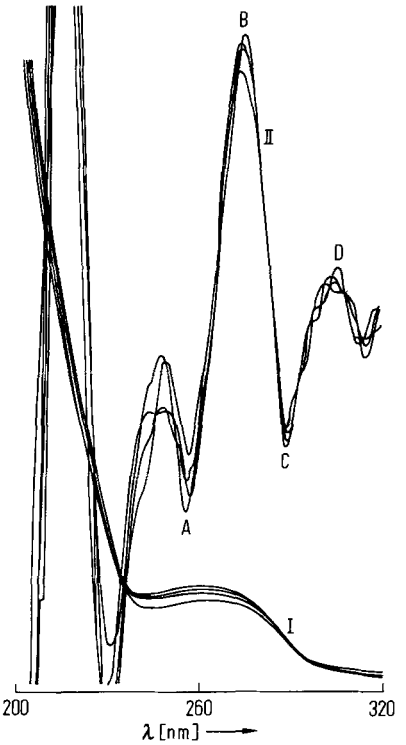


Fig. 14. Characterization of "Vollbier" from various suppliers. I: fundamental spectra (0.4% in H_2O); II: 4th derivative; LTH 1 cm, slit 1 nm, scan rate 5 nm/s. The extrema A, B, C, D, were evaluated.

spectrum. As little as 1 ppm of saccharin can be determined in this way.

Even complicated mixtures such as bottom- and top-fermented beers can be characterized. Whereas up to the third derivative practically no difference can be detected between "Vollbier" (Porter beer) and "Weissbier" (pale beer), this can be done from the fourth derivative spectrum (Fig. 13). It is actually possible to identify the products from several different suppliers (Fig. 14). For this purpose it is useful to establish the ratio $\overline{BC}:\overline{CD}$, this being then multiplied by the factor $\overline{AB}$, which is always typical for each of the two kinds. Under the given experimental conditions these characteristics of all the types of "Weissbier" lie between 25.7 and 31.0, and of "Vollbier" between 33.0 and 37.6.

Similarly, it is possible to examine and determine the protein content of milk types such as untreated cow's milk, uperized milk, and skimmed milk. The HODS method can also be applied *e.g.* to the analysis of unsaturated fatty acids in fats (hexane as solvent).

5.5. Drugs

Cysteamine (2-aminoethanethiol) and vitamin C (ascorbic acid) are used, *inter alia*, for protection against radiation and in the treatment of ketonuria. Both compounds reduce iodine solution. Vitamin C can be determined without interference *e.g.* by the Methylene Blue method, but it is simpler to find the contents of both substances simultaneously from the *fifth*-

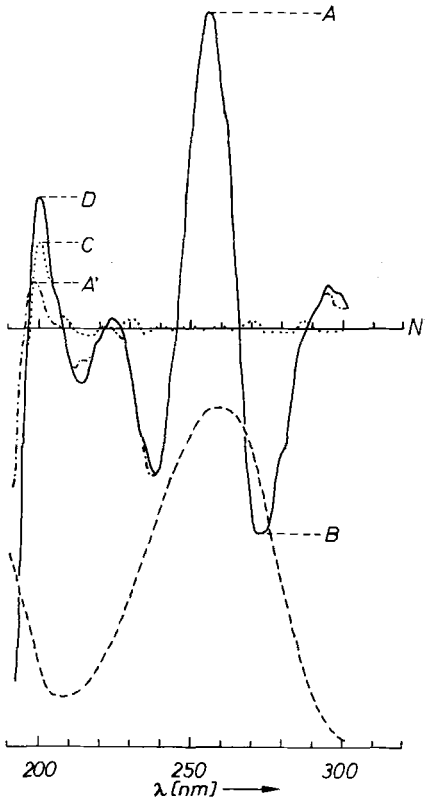


Fig. 15. Simultaneous determination of a mixture of cysteamine (concn. 6 mg/l) and vitamin C (concn. 15 mg/l); LTH 1 cm, slit 1 nm, scan rate 5 nm/s. Fundamental spectrum of the mixture (---); 5th derivative vitamin-C spectrum (-·-·-); 5th derivative cysteamine spectrum (.....); 5th derivative spectrum of the mixture (——). A, A', B, C, D, see text.

derivative spectrum (Fig. 15). Such a high order is necessary here because the cysteine spectrum overlaps a part of the

vitamin C spectrum very unfavorably. However, the objective can be attained by first determining the ratio of $\overline{AB}$ to $\overline{A'N}$ (N = zero line) in the fifth-derivative spectrum of vitamin C, and then recording the fifth derivative of the spectrum of the mixture, calculating the contribution of the vitamin C to the maximum at about 200 nm by means of the ratio determined in the previous experiment and subtracting it ($\overline{DN} - \overline{A'N} = \overline{A'D}$ = cysteamine).

We have also used the HODS method with success in investigations of cortisones, azulenes, plant extracts, and tea infusions.

5.6. Amino Acids

In addition to cysteine which absorbs weakly in the ultraviolet, phenylalanine (Phe), tyrosine (Tyr), and tryptophan (Trp) absorb actively between 200 and 300 nm. Although the individual chromophores can easily be determined, owing to the overlapping of the spectra this cannot be done at all, or only unsatisfactorily, for mixtures of two or three of these amino acids (Fig. 16). It is occasionally possible to determine



Fig. 16. Fundamental spectra of Tyr (---), Trp (-·-·-), and Phe (-···-); concn. 5×10^{-4} mol/l in all cases.

the composition of a binary mixture from the ratio of the extinction coefficients at two wavelengths (*e.g.* for Tyr/Phe at pH 10). The problem can certainly be solved far better by computer analysis of the superposed curves than by means of the extinction ratio, as has been done with success for many other mixtures. *Hirt et al.*[84], *Kienitz*[85], *Neuer*[86], *Lübbers* and *Wodick*[87], *Klabuhn et al.*[88], *Junker* and *Bergmann*[89], and *Fahr et al.*[90] have studied digital multicomponent analysis in detail.

Matsushima et al.[9] have described the investigation of amino acids and native proteins by means of derivative spectrophotometry; they were able by this method to achieve a considerable increase in the sensitivity of the determination of Phe in presence of Tyr and Trp. Further, *Ichikawa*[91] showed that the second derivatives of the spectra of Tyr and Trp do not disturb the characteristic bands in the spectrum of Phe in the 245 to 270 nm region. *Schmitt*[11] draws attention to the broad band at 280 nm, known as the "aromatic peak", which is to be ascribed to Phe, Tyr, and Trp and which shows surprisingly well-developed fine structure in the second derivative spectrum; he also discusses the possibility that the three aromatic amino acids could be determined quantitatively in the presence of one another in unhydrolyzed proteins if the broad maximum were resolved by derivative spectrophotometry.

Our systematic investigations to date have shown that very satisfactory results can be obtained for two-component mixtures within certain molar ratio limits (Table 1).

Table 1. Simultaneous two-component determination of Tyr, Trp, and Phe. Total concentration of the amino acids 5×10^{-4} mol/l.

Molar ratio	Amino acid	pH	Derivative	Max. error [%]
Tyr—Trp				
10:1—2:1	Tyr	7	2nd	96±6
7:1—1:4	Tyr	10	1st	92±5
7:1—1:2	Tyr	10	3rd	105±6
10:1—1:4	Trp	7	1st	106±6
Phe—Tyr				
7:1—1:7	Phe	7	4th	90±4
7:1—1:7	Tyr	7	0th -4th	100±5
Phe—Trp				
4:1—1:4	Phe	7	4th	96.5±4
4:1—1:4	Trp	7	0th—4th	100±5

In the case of three-component mixtures Phe and Trp are best determined from the fourth derivative at pH 7, and Tyr

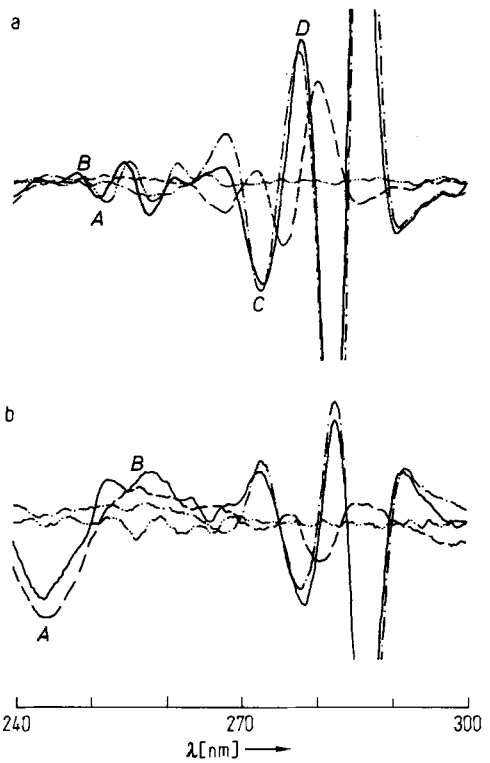


Fig. 17. Simultaneous determination of Phe, Trp, and Tyr (concn. 5×10^{-4} mol/l in all cases). LTH 1 cm, slit 1 nm, scan 2 nm/s range 2*E*; Tyr (---), Trp (-·-·-), Phe (-···-), mixture of Tyr, Trp, and Phe (——); a) 4th derivative, pH 7. $\overline{AB}$ is proportional to the concentration of Phe, $\overline{CD}$ to that of Trp; b) 3rd derivative, pH 10. $\overline{AB}$ is proportional to the concentration of Tyr.

best from the third derivative at pH 10 (total concentration 5×10^{-4} mol/l; Table 2, Figs. 16 and 17). Further experiments

Table 2. Simultaneous three-component determination of Tyr, Trp, and Phe. Total concentration of amino acids 5×10^{-4} mol/l. Molar ratios Tyr:Trp:Phe = 1:1:1, 4:1:1, 1:4:1, 1:1:4, 4:1:4, 4:4:1, or 1:4:4.

Amino acid	pH	Derivation	Max error [%]	
Tyr	10	3rd	Phe:Tyr $\leq$ 4:1	100 ± 10
			Phe:Tyr $\gg$ 4:1	107.5 ± 17.5
Trp	7	1st		112.6 ± 12
		4th		100 ± 10
Phe	7	4th		93 ± 10

are needed to show whether the maximum error of the determination, now $\pm 10\%$, can be reduced.

5.7. Peptides and Proteins

We have also investigated whether Phe, Tyr, and Trp can be determined directly in three-component mixtures of the free amino acids even in unhydrolyzed peptides and proteins. According to our results so far this is not directly possible, at least in aqueous solution. In most cases too low a content is observed if calibration is carried out with the free amino acids. Phe, however, still gives the best values (± 5 to $\pm 10\%$ deviation). Difficulties arise mainly from the differing chemical environment of the chromophore, leading to a shift of the maxima and broadening of the peaks, as well as a change in the ε values. Addition of organic solvents, strongly denaturating substances, or substances which effect uniform solvation and permeation of the molecules (perturbation effect) might lead to more successful results here.

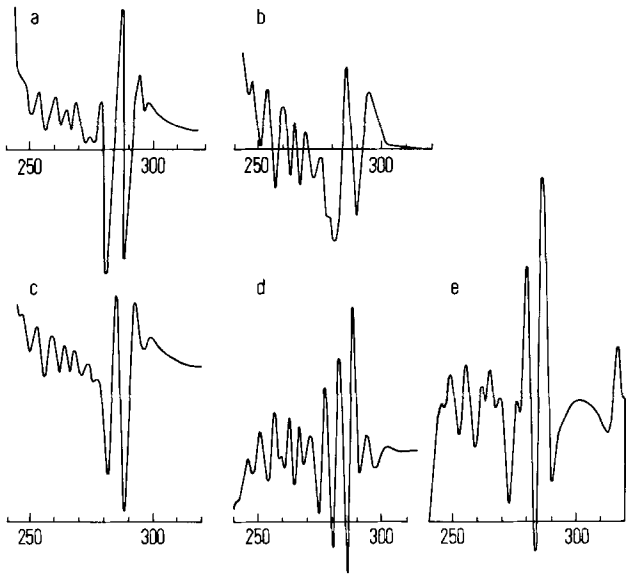


Fig. 18. Examples of "fingerprint spectra", all 3rd derivative, concn. 500 mg/l, LTH 1 cm, slit 1 nm, scan rate 2 nm/s. a) γ-Globulin from bovine serum (inverted); b) catalase (pH 8, inverted); c) fibrinogen (inverted); d) aldolase from rabbit muscle; e) horse heart cytochrome C; numerical values: wavelengths λ in [nm].

Derivative spectrophotometry, particularly of the higher orders, is however very well suited for the provision of "fingerprints" for characterization, purity testing, and identification of proteins with the aid of a spectral catalog. The following small selection of third-derivative spectra may serve as examples: γ-globulin (Fig. 18a), catalase (Fig. 18b), fibrinogen (Fig. 18c), aldolase (Fig. 18d), and cytochrome C (Fig. 18e).

We have also used HODS successfully in the study of protein denaturation (Fig. 19a) and for investigating modified proteins. For example, the acetylation of trypsin can be followed and albumins can be characterized (Fig. 19b). The influence of the solvent on proteins and their structure can also be studied in this way.

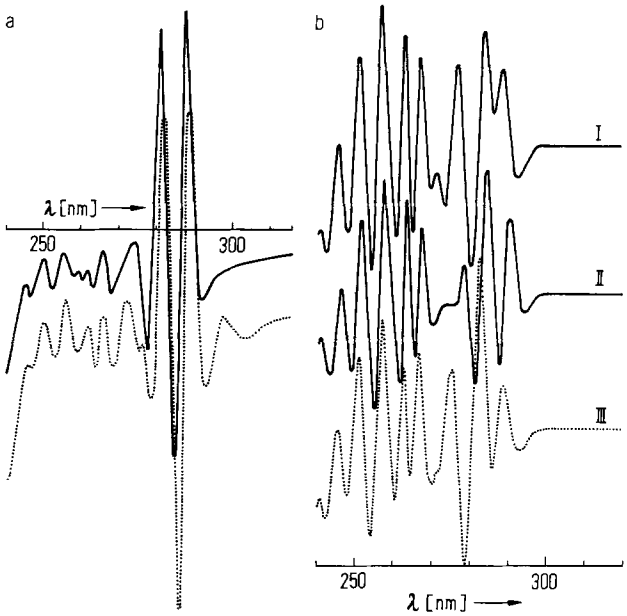


Fig. 19. a) Denaturation of bovine trypsin (concn. 500 mg/l), 3rd derivative; native enzyme (– – –), enzyme denatured in 6 M urea solution (——); LTH 1 cm, slit 1 nm, scan rate 2 nm/s; b) spectra of several albumins (concn. 500 mg/l), 3rd derivative; LTH 1 cm, slit 1 nm, scan rate 2 nm/s; I: bovine albumin, II: hen albumin; III: methylated hen albumin.

5.8. Turbid Solutions, Suspensions, and Emulsions

Turbid solutions and suspended or emulsified solid or liquid materials make spectrophotometric investigations very much more difficult. Because of the scattering that occurs in the UV region in particular, the spectrum of the substance of interest is superimposed on a more or less intense background and, in addition, loses much of its intensity. For example, *Butler* and *Hopkins*[77–79] recommend single-beam instruments for investigating pigments in yeast cells and chloroplasts because of the greater light yield; they eliminate the background by a function simulator[79] or calculate the second and fourth derivatives of the spectrum by an off-line method employing a memory[77, 78].

In our investigations we used a double-beam instrument, the sample and comparison positions of which were immediately in front of the multiplier, whereby it was possible to increase the energy yield considerably for strongly scattering substances.

Depending on the difficulty of the problem we used the third, fourth, or fifth derivative. We studied several types of milk, cream, whey, sour milk, yoghurt and edible curds, and also turbid fruit juices, polysulfides, and kieselgur and bentonite slurries.

5.9. Solids

Higher-order derivative spectrophotometry finds a very interesting and effective application in investigations of highly viscous liquids, gels, and solids.

In the case of solids, for qualitative studies it is sufficient to place the finely powdered sample between two Suprasil plates, in one of which a depression 0.2 mm deep has been cut. It is also advantageous here to use apparatus in which the second sample chamber is immediately in front of the multiplier. A thin layer of paste or highly viscous liquid can be placed directly on a small glass or quartz plate. The same procedure can be used for foils and gels, in which *e.g.* insoluble materials may also be embedded.

Another application is the investigation of paper chromatograms and thin-layer chromatograms. An absorbing position on the foil is found and the derivative spectrum at that point is measured. The unknown compound can then be identified by means of the "fingerprint" and a spectral catalog. Moreover, substances can be enriched by adsorption on a suitable column packing and the solid can then be analyzed as described above.

We have also, as in IR spectroscopy, prepared KBr disks of constant weight (300.0 mg) and compressed them under a constant pressure to ensure constant thickness. The results available so far indicate that the problem of quantification can probably be solved. By standardizing the tableting conditions and averaging several measurements at different tablet positions, we have attempted, for example, to determine the protein content of protein-containing samples directly, without the need for hydrolysis or a determination of the total nitrogen. Figure 20a shows the fundamental spectra of bovine trypsin

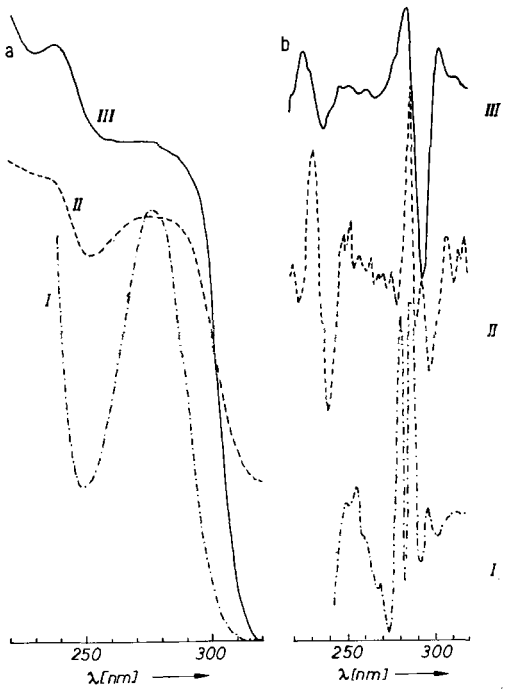


Fig. 20. a) Fundamental spectra of bovine trypsin. I: aqueous solution (concn. 500 mg/l); LTH 1 cm; II: powder, LTH 0.2 mm; III: KBr disk (3 mg of protein in 300 mg of KBr), LTH 0.9 mm; b) 4th derivative of spectra I to III from Fig. 20a. Slit 1 nm, scan rate 2 nm/s.

in aqueous solution, in powder form, and in a KBr disk, all these giving little information; the fourth derivative of the spectra shows the highly differentiated characteristic fingerprints of trypsin (Fig. 20b). We have studied water-insoluble carrier-bound enzymes in the same way.

5.10. Gases and Vapors

Mention should also be made of the application of HODS to the analysis of gases and vapors. For this purpose, for example, a drop of a highly volatile liquid is placed in a tightly closed cell with a ground-in stopper, and is kept in a thermostat at temperatures above *ca.* 20°C; alternatively, the gaseous substances are drawn into the evacuated cell. For continuous investigations the gas or vapor mixture is pumped continuously through a flow-through cell by a peristaltic pump.

Finally, vapors can also be bound to foils coated with an adsorption agent and then be treated as described in Section 5.9.

5.11. Other Fields of Application

We have also applied HODS to the characterization of copolymers and, especially, to the investigation of azopolycarbonates[92]. Preliminary experiments have been encouraging.

Of biopolymers we have studied ribonucleic acids, in addition to the proteins mentioned in Section 5.7.

From the field of clinical chemistry we should mention studies of serum and urine (total porphyrin, proteins, determination of metabolites and traces of drugs).

Since HODS can drastically enhance the sensitivity of many methods of determination, we have been able to use the analog computer with advantage for studying kinetic processes, in particular the kinetics of enzyme reactions and of the thermal decomposition of azo compounds[92].

Finally, mention should also be made of the use of higher-order derivative spectrophotometry for the characterization of column eluates.

For differentiating the elution diagrams themselves we are currently developing an analog differentiator with particularly large differentiation time constants, and this should be useful for processes that occur very slowly.

6. Summary and Prospects

The above examples represent only a small selection from the many diverse possibilities of applying HODS to practical problems. This improved analog on-line analytical technique provides UV/VIS spectrophotometry with a new dimension as regards its ability to provide information, and by relatively simple means it opens new fields of application.

Particular advantages are offered by higher-order derivative spectrophotometry in the following cases: trace analyses, purity testing, quality control, separation of superposed spectra (multicomponent analysis), elimination of background absorption, investigations of turbid solutions and suspensions and of solids, and characterization of individual substances and mixtures.

In addition, derivative spectrophotometry can offer valuable help *e. g.* in the study of reaction kinetics, study of adsorption on surfaces of catalysts or macromolecules, and in the examination of the effects of solvents and chemical surroundings on chromophore groups.

The order of the derivative will vary from [illegible] to case. Optimum conditions are generally reached when all the

shoulders and inflections of a unipolar fundamental spectrum are converted into bipolar maxima and minima. It is then also possible to filter out interfering signals of higher frequency (noise) most successfully, this leading to very good reproducibility and narrow limits of error in spite of high spectral resolution. This is generally achieved with the third, fourth, or fifth derivative. Derivative spectra of still higher order—we have recently checked this up to the ninth order—provide further information only in exceptional cases, since with increasing order the number of extrema and thus the complexity of the spectra increase (which can often be of advantage for fingerprints).

The vigorous development of higher-order derivative spectrophotometry will presumably continue for some time and will lead to new instruments using both the simpler route of on-line analog working and the more expensive method of digital calculations *via* intermediate storage with all their advantages and disadvantages. It is certain that this method, which is so productive of results, will not remain restricted to a few research laboratories but will be increasingly introduced into industrial and teaching laboratories and clinics. From the advantages of higher-order derivative spectrophotometry an expanded range of application can be expected for the otherwise relatively uninformative UV/VIS spectrophotometry, and it will certainly contribute to the solution of many problems that have previously been difficult to deal with.

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Organometallic Syntheses with Diazoalkanes

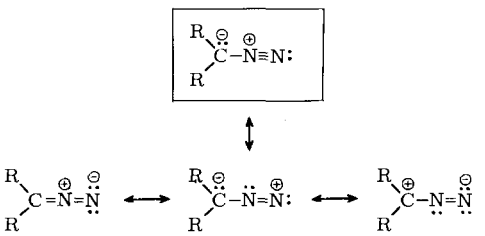
By Wolfgang A. Herrmann[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

In recent years, aliphatic diazo compounds have proved to be more and more versatile as reagents in the preparative chemistry of organometallic complexes. As readily accessible compounds, they are not only suitable for the synthesis of known kinds of metal complexes but also open fresh routes to novel complex systems. The comparatively new field of diazoalkane complex chemistry exhibits numerous unexpected and novel reactions, and introduces interesting and promising aspects into the chemistry of carbonylmetal compounds.

1. Introduction

The discovery of diazoalkanes by *Curtius* and *von Pechmann* is one of the pioneering deeds of organic chemistry. Research performed in the past hundred years led not only to the development of powerful new synthetic methods but also prepared the way for mechanistic studies with the aid of carbene chemistry. Thanks to the classical work of *Meerwein*, *Hine*, *Skell*, and *Doering*, aliphatic diazo compounds were to assume a key role. Progress reports by *Huisgen*[1], *Weygand* and *Bestmann*[2], and *Eistert* and *Regitz*[3, 4] paint an impressive picture



of the preparative versatility of diazoalkane chemistry, while *Kirmse* is concerned primarily with mechanistic aspects of the preparation of carbenes from diazo precursors[5]. A recent monograph describes the properties and syntheses of several hundred diazoalkanes[6].

In organometallic complex chemistry, simple aliphatic diazo compounds have been employed with varying degrees of success, especially for the transformation of metal hydrides into the corresponding alkylmetal compounds. On the basis of these isolated cases it was concluded that diazo compounds are unsuitable for organometallic syntheses owing to their susceptibility to catalytic decomposition. Hence attempts to stabilize carbenes by metals ceased all too prematurely. However, there is hardly a better approach to that goal than by catalytic, photochemical, or thermal decomposition of diazoalkanes. Production of transition metal-dinitrogen complexes should also be possible with diazo reagents.

Surveys by *Fischer*[7], *Lappert*[8], and *Cotton*[9] reveal the great importance of transition metal—carbene complexes in organometallic chemistry. Progress reports by *Sellmann*[10] and *Chatt*[11] show that transition metal—dinitrogen complexes constitute a highly topical research field in connection with nitrogen fixation. The synthesis of members of these two classes of compounds was the initial aim of our studies. However, we soon recognized that diazoalkanes readily form many other complex compounds, some containing nitrogen and others containing none. Meanwhile, the synthetic potential of aliphatic diazo compounds has been utilized for producing a variety of ligand systems on transition metal substrates.

2. Transition Metal—Carbene Complexes from Diazoalkanes

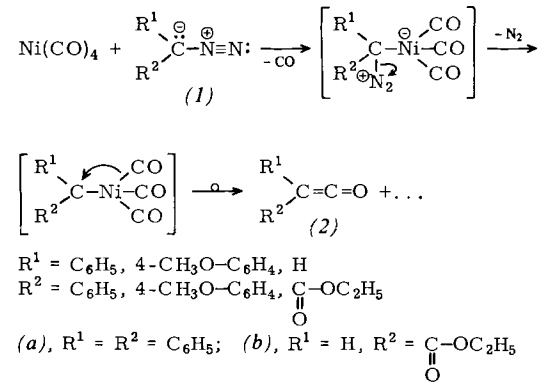
2.1. Historical Background

The catalytic action of numerous transition metal substrates on the decomposition of almost all aliphatic diazo compounds has been known since the early days of diazoalkane chemistry. Thus the addition of copper powder or of silver compounds, such as Ag_2O or $[Ag\{N(CH_3)_3\}_2]^+OCOC_6H_5^-$, is still used in the Wolff rearrangement[1, 3, 12]. At a very early stage, carbene complexes were assigned a crucial role in metal-induced diazoalkane reactions[13]. Although many years were to pass before the synthesis and isolation of stable transition metal—carbene complexes from aliphatic diazo compounds was demonstrated[14], there was no lack of experimental results to sustain the hypothesis of unstable diazoalkane—metal or carbene—metal intermediates.

Turning their attention to the question of carbonylation of carbenes, originally raised by *Staudinger*[15], *Rüchardt* and *Schrauzer* were the first to prove the general ability of carbenes to form complexes[16]. These authors examined the action of tetracarbonylnickel on diphenyldiazomethane *(1a)* and some of its homologs and on ethyl diazoacetate *(1b)*; they found that excess $Ni(CO)_4$ in ethanol transforms *(1a)* into diphenylketene *(2a)* in 73% yield. The initial step of the reaction possibly involves a nucleophilic attack on $Ni(CO)_4$ by the diazoalkanes *(1) via* their basic C atom, leading to carbonyl substitution. Subsequent exothermic elimination of nitrogen, which now has the character of an aliphatic diazonium group, apparently yields a highly unstable carbene complex, which decomposes to a ketene *(2)* and a metal carbonyl fragment. Similar reaction steps are also assumed to occur in the carbonylation of olefins and acetylenes.

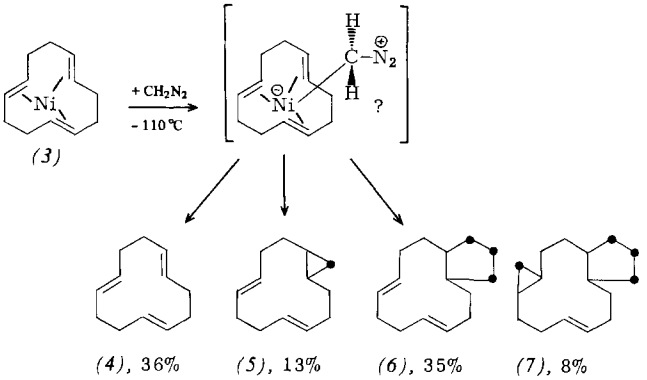
Although stable nickel—carbene complexes could not be synthesized in this way, *Rüchardt* and *Schrauzer* had already

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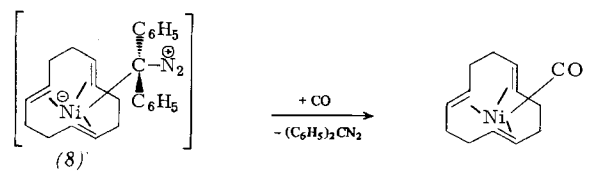
mentioned that dπ(metal)—pπ(carbene) interactions might have an important function in the stabilization of carbenes[16]. Predictions of bond stabilization in complexes with conjugated carbenes by mesomeric delocalization of the positive charge on the carbene were also confirmed by subsequent organometallic studies. In spite of further evidence[17], carbene carbonylation long remained unconfirmed until the recent successful high-pressure carbonylation of diphenylcarbene—manganese complexes to give diphenylketene derivatives (see Section 2.3)[18]. Carbene carbonylation with subsequent hydrogenolytic degradation of the ketene complexes is a model system for the formation of oxo products in the Fischer-Tropsch synthesis[18a].

Investigations by *Wilke* and his research team showed that all-*trans*-1,5,9-cyclododecatrienenickel, (*t,t,t*-CDT)Ni *(3)*, reacts with excess diazomethane even at −110 °C with vigorous evolution of gas and deposition of nickel[19]. Apart from the free ligand cyclododecatriene *(4)*, new bi- and tricyclic systems could be isolated and quantitatively determined: bicyclo[10.1.0]trideca-4,8-diene *(5)*, bicyclo[10.3.0]pentadeca-4,8-diene *(6)*, and tricyclo[11.3.0.0^{4,6}]hexadec-9-ene *(7)*.



(4), 36% *(5)*, 13% *(6)*, 35% *(7)*, 8%

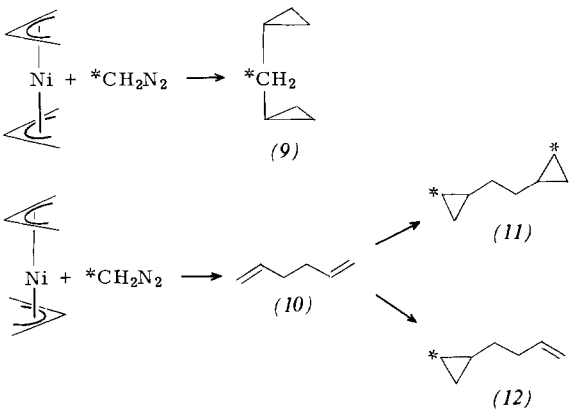
Formation of multiply methylenated reaction products has not otherwise been observed in diazomethane chemistry. The idea that the reaction is initiated by nucleophilic attack by diazomethane on the free coordination site of the metal center is supported both by the failure of methylenation to occur on use of the coordinatively saturated carbonyl derivative (*t,t,t*-CDT)Ni(CO) and by the formation of a 1:1 adduct *(8)* of (*t,t,t*-CDT)Ni *(3)* and diphenyldiazomethane, which is stable below −30 °C[19-21].



(8)

Further studies of the diazomethane reactions of *t,t,c*-, *t,c,c*-, and *c,c,c*-1,5,9-cyclododecatrienenickel led to similar results. The yields of methylene addition products and the yield of the product with annelated five-membered ring decrease sharply along the series given. In the case of the *t,t,c*- and *t,c,c*-isomers, methylene adds stereospecifically to a *trans* double bond[20,21].

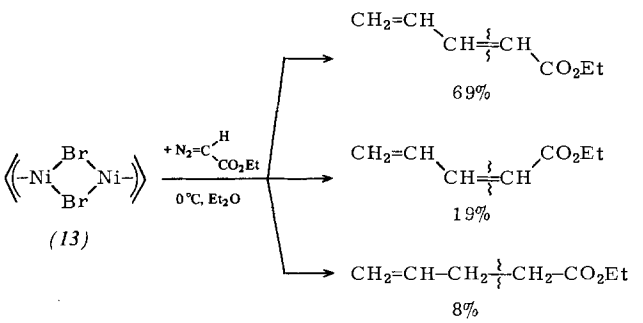
Bis(η^3-allyl)nickel displays a pronounced conformational control of reactivity towards diazomethane[22-24]. The *cis* isomer forms exclusively dicyclopropylmethane *(9)*; under the same conditions (−78 °C) the *trans* isomer gives a mixture of 1,5-hexadiene *(10)*, 1,2-dicyclopropylethane *(11)*, and 4-cyclopropyl-1-butene *(12)*. Reaction with [D$_2$]diazomethane furnished proof that the two allyl ligands first undergo linear dimerization—probably in the coordination sphere of the metal—and are then "cyclopropanated". Deuterium-labeling



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

experiments also showed that the product ratio (GC-MS) *(9)*:Σ*(10)* + *(11)* + *(12)* is in exact agreement with the *cis/trans* ratio of the substrate (η^3-C$_3$H$_5$)$_2$Ni as determined by ^{1}H-NMR spectroscopy in the temperature range examined (−30 to −78 °C). Although this represented the first chemical proof of the existence of *cis/trans* isomers of bis(η^3-allyl)nickel, it provided little information about the nature of the intermediates involved in this interesting sequence of reactions. Primary adducts of diazomethane and unstable carbene complexes will certainly play a role.

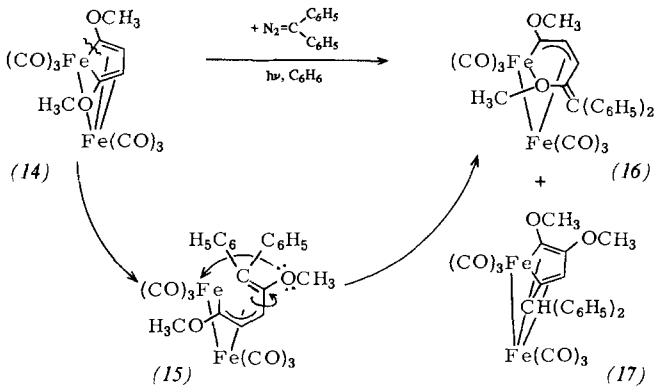
Butadiene derivatives are formed on reaction of bis(η^3-allyl-μ-bromo)nickel *(13)* with ethyl diazoacetate[25]. Even at 0 °C, the reaction is so fast that evolution of gas is complete within



(13)

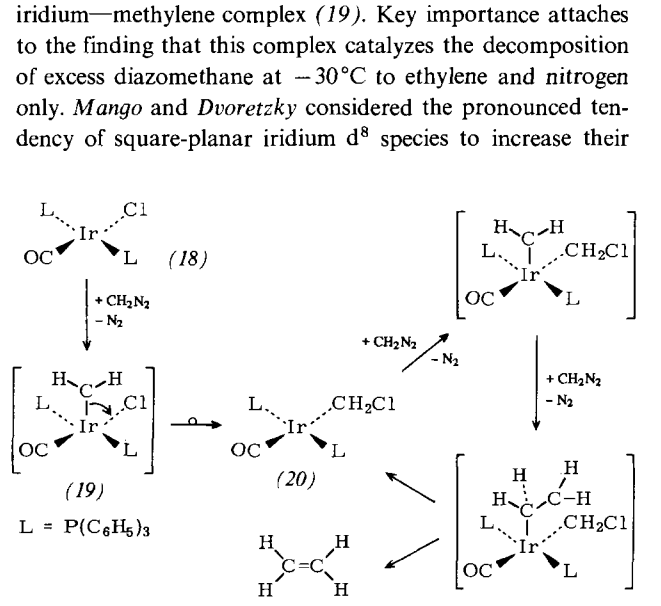
seconds. A carbenoid 1:1 complex is again proposed as key intermediate: it is assumed to transform into a σ-allyl complex "L$_x$Ni—CH(CO$_2$Et)C$_3$H$_5$" which then undergoes β-elimination.

Carbene insertion into the Fe—C bond has been accomplished with the carbonyliron complex *(14)* without spontaneous decomposition of the primary adduct[26]. The structure (X-ray) of the resulting product *(16)* is compatible with (Fe—C)carbene insertion followed by rotation of the open-chain allyl-ene system *(15)* about the C—C single bond. Formation of the complex *(17)* is less readily understandable.



Among the ferrocene-type sandwich complexes, nickelocene has the greatest catalytic effect on the polymerization of diazomethane and ethyl diazoacetate[27]. Low-molecular products (oligomers, insertion products) are not formed, in contrast to the reactions considered so far. A nickel—methylene complex $(C_5H_5)_2NiCH_2$ is postulated[27] in connection with the formation of polymethylene from diazomethane, a fast reaction even at −78 °C. The rate of polymerization is much higher than with conventional catalysts such as powdered copper or iron-chelate complexes.

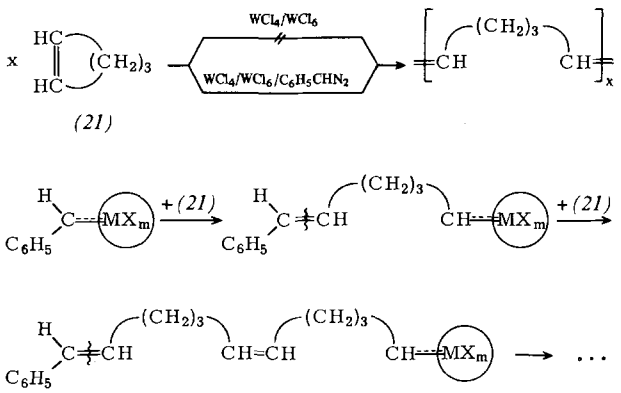
An almost quantitative precipitate of polymethylene is rapidly obtained on treating solutions of diazomethane in benzene or chloroform with catalytic amounts of the Vaska compound *(18)* at room temperature[28]. However, treatment of a diethyl ether suspension of complex *(18)* with diazomethane at −30 °C gives a crystalline air-stable product containing no polymethylene. The compound, which is unstable in solution, proves to be the square-planar carbene insertion product *(20)*; it might be formed *via* the hypothetical five-coordinate iridium—methylene complex *(19)*. Key importance attaches to the finding that this complex catalyzes the decomposition of excess diazomethane at −30 °C to ethylene and nitrogen only. *Mango* and *Dvoretzky* considered the pronounced tendency of square-planar iridium d^8 species to increase their coordination number from four to five without any formal change in oxidation state to justify their proposed mechanism for ethylene formation shown here in simplified terms.



Deuterium-labeling experiments convincingly demonstrate that the initially formed Ir—CH_2Cl group in *(20)* does not participate in methylene dimerization[28]. In this context, the work of *Meerwein* and *Rathjen* should be called to mind: they too could detect only ethylene on $TiCl_4$-catalyzed decomposition of diazomethane[29].

Diazoalkanes were also instrumental in the recent demonstration that olefin metathesis proceeds not by *Calderon*'s four-center mechanism but instead *via* carbene complexes. *Dolgoplosk et al.* attributed an initiator role to several aliphatic diazo compounds in the special case of ring-opening cycloalkene polymerization[30–35]: thus just a few drops of a 0.02 M toluene solution of phenyldiazomethane suffice to polymerize cyclopentene *(21)* or 1,5-cyclooctadiene with WCl_6 (molar ratio 1000:1 or 500:1, respectively) within a few minutes to polyalkenamers of extremely high molecular weight[31,32].

Similar observations have been reported[31] for the heterogeneous system with WCl_4 as catalyst. The failure of ring-opening and polymerization to occur in the absence of phenyldiazomethane demonstrates that the actual catalytic species is a tungsten—phenylcarbene complex formed by decomposition of phenyldiazomethane in the coordination sphere of the metal which initiates reaction with the (π-coordinated) cycloolefin.



The carbene intermediate in polymerization reactions of this kind has not been rigorously established; however, it appears highly likely in view of the results obtained with olefin metathesis in the stricter sense[36–38] and especially the mechanistic studies performed by *Katz et al.*[39].

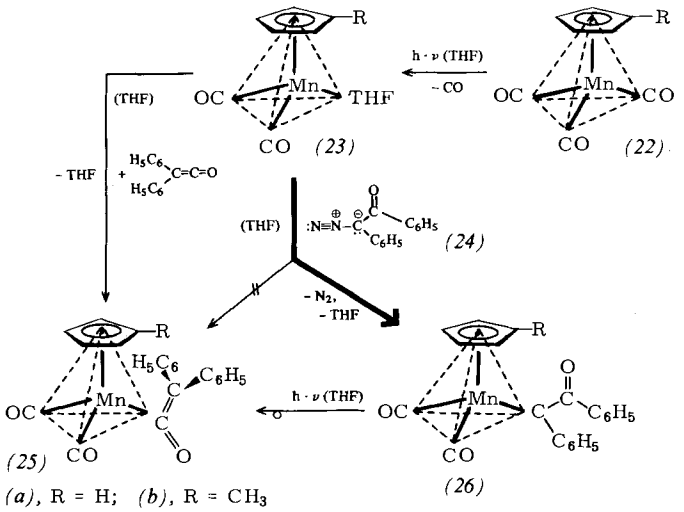
2.2. Statement of Problem

Although the cases cited and other work surveyed in 1973 by *Lappert*[40] suggest that diazo compounds are basically suitable as precursors of transition metal—carbene complexes, the instability of the postulated intermediates long stood in the way of more thorough and synthetically oriented studies. Moreover, it was formerly held, quite justifiably at that time, that only heteratom-stabilized carbene complexes are sufficiently stable to be unequivocally characterized and handled on a preparative scale. Precisely the alkoxy- or bis(alkoxy)diazomethanes required for their synthesis number among the least stable diazoalkanes and cannot be isolated pure.

2.3. Preparative Work

The methodological feature of the synthesis of transition metal—carbene complexes from diazoalkanes is the exchange of a readily replaceable two-electron ligand of the organometallic starting compound for the CRR′ unit of the diazo precursor. The reaction conditions should be as mild as possible to avoid uncontrolled decomposition of the diazoalkane.

The action of, *e. g.* benzoyl(phenyl)diazomethane (azibenzil) *(24)* on the manganese-THF complexes *(23a)* and *(23b)* at room temperature yields the hitherto inaccessible air-stable benzoyl(phenyl)carbene complexes *(26a)* and *(26b)*[14,41].



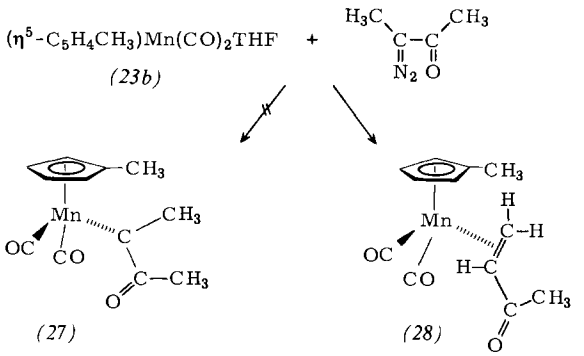
(a), R = H; *(b)*, R = CH_3

The formation of these two carbene complexes is all the more surprising in view of the fact that Wolff rearrangement of aliphatic diazoketones is usually so fast that the keto carbenes formed as reactive primary fragments[*] can be trapped only under special conditions[4,12,42]. While carbenes generated, *e. g.* photolytically by nitrogen elimination from *ortho*-quinone diazides, can be saved from intramolecular rearrangement by 1,3-dipolar cycloadditions[43], direct trapping of benzoyl(phenyl)carbene has so far proved impossible.

Remarkably, the reaction of azibenzil *(24)* with the manganese-THF complexes *(23)* does not afford coordination compounds *(25)* of diphenylketene. This means that the Wolff rearrangement of the diazoketone is quantitatively stopped after the rate-determining step of nitrogen elimination. The keto carbene, which is, so to speak, conserved in the transition metal complex *(26)*, can nevertheless be induced to undergo intramolecular rearrangement: UV irradiation gives the π-diphenylketene complexes *(25)*[41,44]; X-ray structure analyses are also available for *(25a)* and *(26a)*[45,46].

In similar manner, the diarylcarbene complexes of type *(26)*, with R = H, CH_3, and C(*p*-$R^1C_6H_4$)(*p*-$R^2C_6H_4$) in place of the keto carbene (R^1, R^2 = H, CH_3, Cl, NO_2, OCH_3) are formed from diphenyldiazomethane and its derivatives in yields of up to 82 %[41]; ethyl (4-nitrophenyl)diazoacetate gives the corresponding ester—carbene complexes[47].

Complications occur when secondary reactions of the carbene receive catalytic support. Thus intermolecular ketazine formation from diaryldiazomethane derivatives can never be completely suppressed, while intramolecular rearrangements come to the fore with alkyl-substituted α-diazo ketones. For example, the expected acetyl(methyl)carbene complex *(27)* is absent from the reaction products of 3-diazo-2-butanone with complex *(23b)*; instead, the isomeric 3-buten-2-one derivative *(28)* is formed, at least formally, by an H shift within the carbene fragment[41].



The realistic nature of the proposed reaction route is supported by independent work by *Fischer* and *Held*, who likewise obtained only the corresponding π-olefin complexes on attempted synthesis of [alkyl(phenyl)carbene]pentacarbonyltungsten complexes[48]. We cite these examples because the linkage of carbene and olefin complexes is of cardinal importance in current research on olefin metathesis.

Transfer of the diazo nitrogen from diazoalkanes to metal centers has also been accomplished in some cases: reactions of 1,1,1-trifluorodiazoethane and *(23)* give the dinuclear dinitrogen complexes μ-$N_2[(\eta^5\text{-}RC_5H_4)Mn(CO)_2]_2$ of known structure (X-ray); its formation cannot involve free nitrogen liberated catalytically or thermally from the diazoalkane[49]. Initial end-on coordination of the diazoalkane $[RR'C{=}N{=}N \rightarrow ML_x]$ is assumed to be followed by elimination of the carbene which undergoes ready intramolecular stabilization. Ethyl diazoacetate reacts with $[Ru(NH_3)_5H_2O]^{2+}$ in a neutral aqueous medium to give a mixture of $[Ru(NH_3)_5N_2]^{2+}$ and $[(NH_3)_5Ru{-}N{\equiv}N{-}Ru(NH_3)_5]^{4+}$[50].

2.4. Classification of the Diazo Method

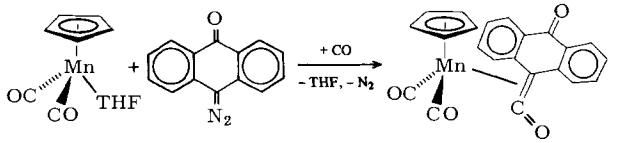
Great activity in the field of transition metal—carbene complexes has led to the development of numerous preparative methods based essentially upon four synthetic principles (cf. [7-9,51]): 1) Formation of the carbene ligand at the metal substrate by refunctionalization of an existing metal—carbon bond; 2) exchange of substituents on the (metal—)carbene system; 3) carbene transfer $L_xM{-}CRR' \rightarrow L_yM'{-}CRR'$; 4) introduction of a carbene ligand *via* suitable carbene precursors into a metal substrate.

The diazo method considered here belongs to the last-named group. The method exploits the *a priori* most accessible possibility of synthesizing transition metal—carbene complexes; the intact carbene ligand is transferred from an aliphatic diazo compound onto complex substrate. Closely related syntheses of transition metal—methylene complexes are known (cf. Section 4).

[*] Concerning the role of the oxirene intermediate present in equilibrium with the ketocarbene in the photochemical Wolff rearrangement, see [12].

3. Transition Metal—Ketene Complexes from Diazoalkanes

In some cases, metal-induced diazoalkane fragmentation proceeds beyond complexation of the carbenes to η^2-ketene complexes; the product yields increase drastically on working in a CO atmosphere[52]. The reaction of 10-diazoanthrone *(29)* may be cited as an example. Although complete elucida-



(23a) *(29)* *(30)*

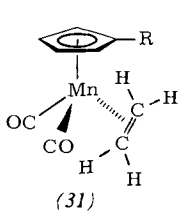
tion of the reaction course must wait for ^{13}CO-labeling studies, it is nevertheless very probable that the η^2-ketene complexes *(30)* are formed by carbonylation of the initially formed metal carbenes with external carbon monoxide. This possibility of reaction points to a new entry to the class of η^2-ketene complexes[51], of which only scattered examples were previously known, especially in those cases where the instability of the free ketenes precludes direct synthesis.

4. Syntheses of Transition Metal—Methylene Complexes

Hundreds of stable transition metal—carbene complexes have been prepared since the discovery of the first representative by *Fischer* and *Maasböl* in 1964. Surprisingly then, there is a comparative lack of knowledge about carbene systems whose central carbon bonds not to just one metal atom but bridge *two* metal-complex fragments. Apart from a few exceptions, compounds of the type μ-$CRR'[ML_x]_2$ have only been isolated in yields below 5% as products of rather unclear reactions[51]. Aliphatic diazo compounds now provide a pathway to numerous highly stable μ-methylene complexes[*] belonging to the carbonyl—manganese, —iron, —cobalt, —rhodium, and —osmium series, which also include the first examples of bridged CH_2 complexes[53,58].

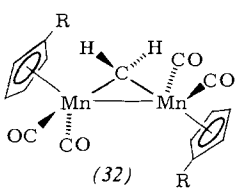
4.1. Incorporation of Methylene into Manganese Complexes

Depending upon the molar ratio of reactants, the reactions of diazomethane with manganese—THF complexes *(23)* give a mixture of the olefin complexes *(31)* and the μ-methylene complexes *(32)*[53]. The *trans* configuration[54,125] deduced



(31)

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



(32)

$(\eta^5\text{-}RC_5H_4)Mn(CO)_2CH_2$

(33)

for the latter from spectroscopic results was confirmed by X-ray structure analyses. Although the π-ethylene complexes are more readily accessible photochemically directly from the tricarbonylmanganese complexes *(22)*, their formation should be noted in this context inasmuch as the thermal decomposition of diazomethane does not[4] lead to ethylene, and the transition metal-catalyzed decomposition of diazomethane does so but rarely[28,29].

Surprisingly, the mononuclear carbene complexes *(33)* expected from the results obtained with diphenyldiazomethane and its *p*-substituted derivatives are not formed. Product analysis supports the proposed intermediacy of the methylene—manganese complex *(33a)*. If it fails to react with another species, then it decomposes on heating to room temperature. However, if an excess of diazomethane is present then it preferentially forms the monomeric ethylene derivative *(31a)*, whereas the carbene species *(33a)* reacts in the presence of the reactive complex substrate *(23a)* to form the μ-methylene complex *(32a)*.

The structural parameters of the prototype compound *(32b)* (Fig. 1) synthesized by the diazo method are characteristic of all transition metal—methylene complexes: the cyclopropane-like Mn—CH_2—Mn skeleton has an angle of 86.9° at the CH_2 bridge[125]; the range between 75 and 90°[63] is typical for analogous compounds. Strikingly, M—CH_2—M and M—CO—M groups always occur together with additional metal—metal bonds. *Hofmann* was able to demonstrate by theoretical calculations (EH procedure) for the first time that μ-methylene complexes are to be regarded electronically as dimetallacyclopropanes and exhibit considerably greater negative charge at the quasi-saturated bridging carbon atom than carbene complexes. The (distorted) tetrahedral configuration of the methylene bridges is in accord with the results of MO calculations[126].

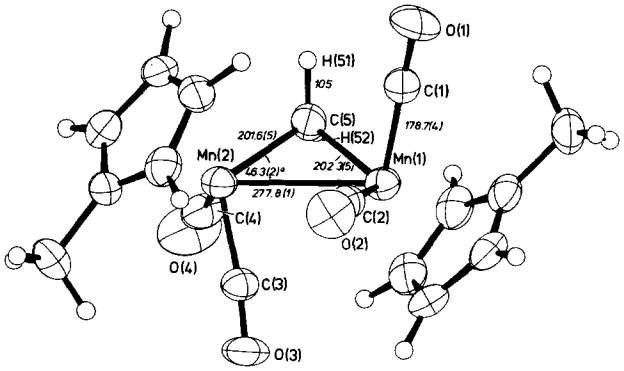


Fig. 1. ORTEP representation of μ-methylene-bis[dicarbonyl(η^5-methylcyclopentadienyl)manganese] *(Mn—Mn) (32b)*. Apart from the hydrogen atoms, the thermal ellipsoids correspond to 50% probability. $R(F)=4.86\%$, $R_w(F)=4.86\%$. Bond lengths in pm.

4.2. μ-Methylene—Cobalt and —Rhodium Complexes

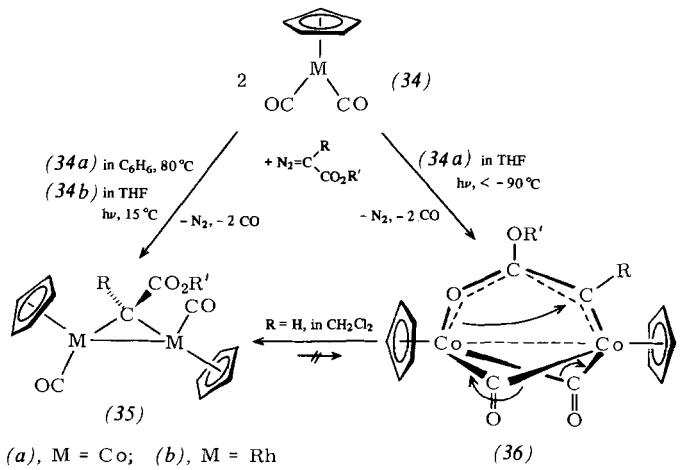
Dicarbonyl(η^5-cyclopentadienyl)cobalt *(34a)* and the homologous rhodium compound are further complex components for the preparation of carbene derivatives. Fast exchange of one of the two carbonyl groups for analogous ligands has been established[5] for both compounds by CO

[*] Concerning the problem of carbene/methylene nomenclature, cf. [51].

exchange experiments and by the kinetic data of carbonyl substitution of phosphanes—this is an important prerequisite for the introduction of CRR′ ligands into carbonylmetal compounds by the diazo method.

4.2.1. Complexes of Type *(35)*, M = Co, Rh

As expected, the cobalt complex *(34a)* reacts smoothly with diazoacetic ester and diazomalonic ester reagents in boiling benzene to give the dinuclear complexes *(35a)* with bridging carbene ligands[56]. The rhodium complex *(34b)* can be transformed photochemically into the corresponding derivatives *(35b)*[57]. X-Ray structure analyses on *(35b)* with a methylene and on *(35a)* with a 1,3-dioxoindan-2-ylidene bridge (in place of R—C—CO_2R') show the carbene C atoms to have a strongly distorted tetrahedral configuration[57a, 58, 59].



(a), M = Co; *(b)*, M = Rh

(36) → *(35a)*, R = H, R′ = C_2H_5: $k = (3.80 \pm 0.03) \cdot 10^{-4}\ s^{-1}$ (17.3 ± 2 °C)
$\Delta G^{\neq} = 21.5 \pm 0.5$ kcal K^{-1} mol^{-1}

(36) → *(35a)*, R = H, R′ = $C(CH_3)_3$: $k = (5.19 \pm 0.23) \cdot 10^{-4}\ s^{-1}$ (29.3 ± 2 °C)
$\Delta G^{\neq} = 22.3 \pm 0.6$ kcal K^{-1} mol^{-1}

The primary reaction step must be either a) dissociation of *(34)* to give the highly reactive fragments (η^5-C_5H_5)M(CO), whose existence is regarded as definite at least under photolysis conditions in the absence of other reactants[60, 61], or b) a direct nucleophilic attack of the diazo compound on the coordinatively unsaturated complex *(34)*. In neither case is it known at what stage the diazo nitrogen is released.

In addition to its synthetic exploitation, this class of compounds has already been the subject of thorough spectroscopic studies. In a detailed mass-spectrometric analysis *Mayer* was able to demonstrate the occurrence of interesting carbene reactions which are unknown for mononuclear carbene complexes[62]. CO exchange phenomena in μ-CH_2[(η^5-C_5H_5)Rh(CO)]$_2$ are presently being studied with the aid of ^{13}C-NMR spectroscopy by *Cotton et al.*, whereas *Bau et al.* are presently performing a neutron diffraction study on the same compound.

The μ-methylene complexes now available in large numbers by the diazo method can be distinguished by their ^{13}C- and ^{1}H-NMR parameters from related complexes L_xM—CH_3 and L_xM—$(CH_2)_n$—ML_x ($n \geq 3$) and from the carbene complexes L_xM—CH_2 (also with R in place of H), as is apparent from a comparison of the typical resonance regions for the methylene and methyl ligands[53, 56–58, 131]:

	$\delta(^{13}C)$	$\tau(^1H)$
L_xM—CH_3	−30... 5	9...11
L_xM—$(CH_2)_n$—ML_x	0... 10	8... 9
μ-$CH_2[ML_x]_2$ (*M*—*M*)	100...190	4... −0.5
L_xM—CH_2	240...370	1... −1

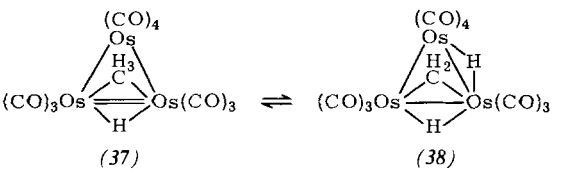
4.2.2. Complexes of Type *(36)*

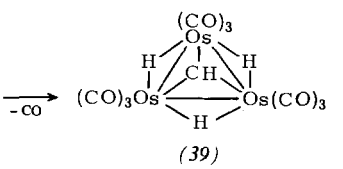
Low-temperature photolysis of diazoacetic ester compounds with the cobalt complex *(34a)* gives both the μ-methylene complexes *(35a)* already described and the isomers *(36)*.

The low-temperature products *(36)* possess two carbonyl bridging ligands as well as a μ-alkoxycarbonylcarbene group, which is attached to both metal centers *via* the carbene carbon *and* the carbonyl function. Most probably, the heat-sensitive products *(36)* are intermediates in the synthesis of complexes *(35a)*, to which they undergo quantitative and irreversible rearrangement with restructuring of the μ-carbene ligand and simultaneous rupture of the carbonyl groups[63]. IR and ^{1}H-NMR kinetic studies show this hitherto unknown type of isomerization to be a first-order reaction. Ligand exchange reactions prove the intramolecular nature of these scrambling processes[63].

4.3. A μ-Methylene—Osmium Cluster

Applying the diazo method to the trinuclear carbonylosmium hydride $H_2Os_3(CO)_{10}$, *Shapley et al.* were recently able to synthesize the cluster molecules *(37)*—*(39)*, of which the μ-methyl derivative *(37)* and the μ-methylene complex *(38)* are in mutual equilibrium. The μ_3-methylidine cluster *(39)*

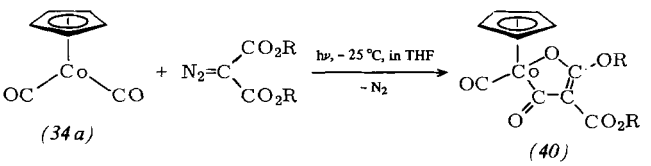




is formed irreversibly from a mixture of *(37)* and *(38)* in xylene at a temperature of 110 °C[127]. The tautomerism of type M(CH_3) ⇄ HM(CH_2) first detected in this case is of importance in mechanistic interpretation of the reactions of hydrocarbons on metal surfaces and associated chemisorption problems[128].

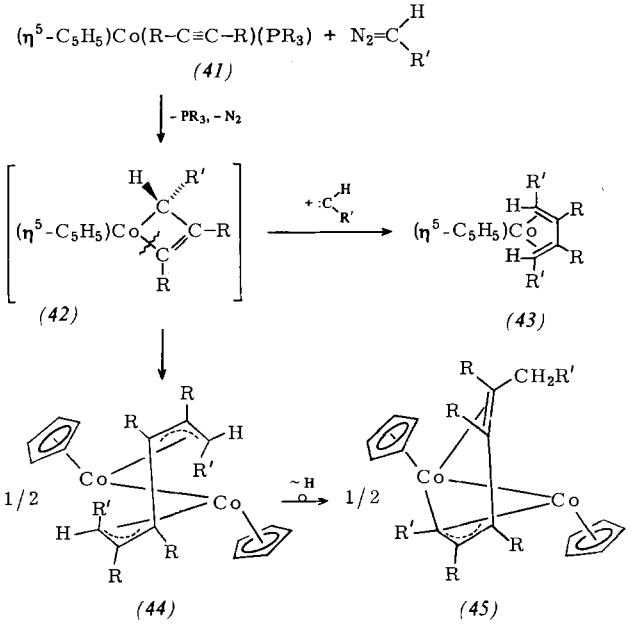
5. Addition of Carbenes to Organometallic Compounds

The bis(alkoxycarbonyl)carbenes formally derived from diazomalonic ester substrates can be added photochemically



to the organometallic component *(34a)* without fragmentation of the latter to give the metallacycle *(40)*: the coordination number of the metal center increases, by coordination of a carbonyl oxygen atom of the carbene unit to the metal and transformation of a M—CO group into a M—acyl function, until it is ultimately in the preferred tetrahedral environment[64,65]. These novel [2+3]-carbene additions should become important in the construction of further five-membered metallacycles.

Reactions of diazoacetic ester derivatives with the acetylene—cobalt complex *(41)* probably proceed both *via* the carbene and *via* metallacyclic intermediates. Formation of the stable end products *(43)*—*(45)* is interpreted in terms of carbene insertions or dimerizing ring opening *via* the common intermediate *(42)*, a 1,6 hydrogen shift of unknown mechanism being invoked to explain formation of *(45)* from the *syn,anti-* and/or *syn,syn* isomer of *(44)*[129]:

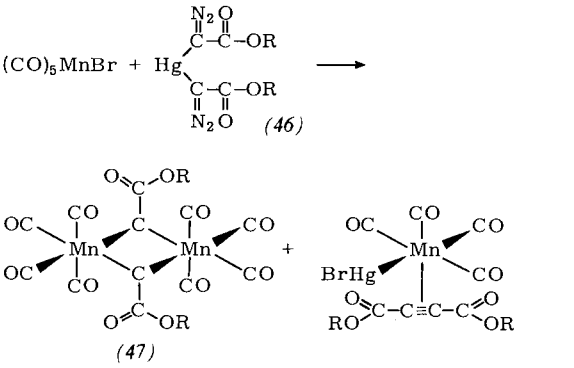


R = C_6H_5; R' = CO_2CH_3, $CO_2C_2H_5$, $CO_2C(CH_3)_3$

6. Organometallic Diazoalkanes; Complexation of Alkoxycarbonylcarbynes as Bridging Ligands in Carbonylmetal Systems

Although *Buchner* synthesized bis(ethoxycarbonyl-α-diazomethyl)mercury *(46a)* as the first metal-containing diazo compound over 80 years ago, metallodiazoalkanes played a very minor role for many decades in the enormous advances of preparative diazoalkane chemistry. Meanwhile, the lithium, silver, mercury, germanium, and tin derivatives are known to be valuable intermediates for the synthesis of homologous diazoalkanes[66]. Moreover, *Lorberth et al.* have very recently developed facile and universally applicable syntheses of a plethora of singly and doubly metalated compounds of type $(L_xM)(R)C{=}N_2$ and $(L_xM)_2C{=}N_2$[67].

Once *Strausz* and *Skell* had found that not only mercury-containing carbenes $R^1(R^2Hg)C$: but also carbynes $R^1{-}\dot{C}$: can occur as intermediates on photolysis of α-mercuriodiazoalkanes[68–72], the scene was set for the first attempts to transfer the carbynes to complex substrates. Starting from the mercury derivatives of diazoacetic esters, it proved possible to prepare, *e.g.*, dinuclear carbonylmanganese complexes *(47)* containing μ-methylidyne ligands[*][74,75].

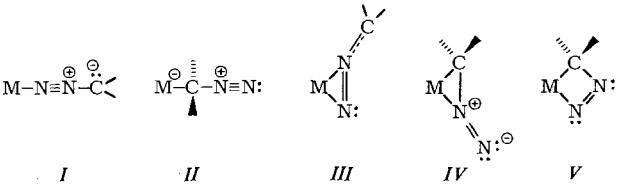


(a), R = C_2H_5; *(b)*, R = $C(CH_3)_3$

This facile method of carbyne (methylidyne) transfer has so far attracted little attention, and its mechanism has not yet been elucidated. In view of the large number of heterodiazoalkanes now available, it holds promise for the synthesis of other μ-methylidyne or carbyne complexes.

7. Transition Metal—Diazoalkane Complexes

The complexation properties of diazoalkanes is of considerable importance in mechanistic discussions on the reactions of organometallic compounds with diazoalkanes, for in most cases the structurally intact diazo component is most likely initially attached to the metal center. As heterocumulene systems, $RR'C{=}N_2$ molecules possess several "basic" functions capable of coordination. Considering just the possible 1:1 products of heteroatom-free diazoalkanes, five more or less realistic structural models can be enumerated: the diazoalkane can be attached to the metal as a monodentate ligand bonding *via* the terminal N atom *(I)* or *via* the central C atom *(II)* or as a η^2 ligand *via* a π-function [N=N *(III)*, C=N *(IV)*], and possibly also after the manner of a 1,3-cycloadduct *(V)*. Some of these possibilities are considered in a recent review[76].

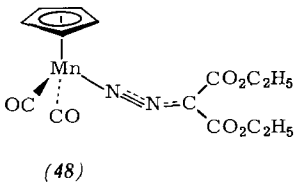


I *II* *III* *IV* *V*

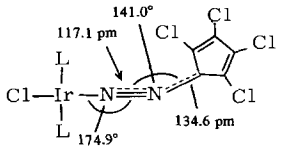
In *type I*, the diazo compound is bonded *via* its terminal nitrogen atom to the central metal. This kind of coordination is less favored, owing to the relatively low energy level of the relevant orbital. Nevertheless, *end-on* attachment of neutral diazo molecules to metal centers has been accomplished in two cases: diethyl diazomalonate is bonded remarkably strongly in the carbonyl manganese complex *(48)*; it can only be displaced by carbon monoxide under high pressure[77]. The analogous compound *(49)*, likewise accessible by direct ligand exchange and which has been examined by X-ray anal-

[*] Concerning carbyne/methylidyne nomenclature, cf. [51]. For a survey of the preparation and properties of carbyne complexes, cf. [73].

ysis, contains tetrachlorodiazocyclopentadiene as a ligand with a nonlinear skeleton which is replaceable by CO or SO_2[130]. Only slight π backbonding by neutral diazo ligands N_2R, as compared with the formally cationic alkyl- or phenylazo groups N_2R^+, is deduced from the observed bond lengths[130].

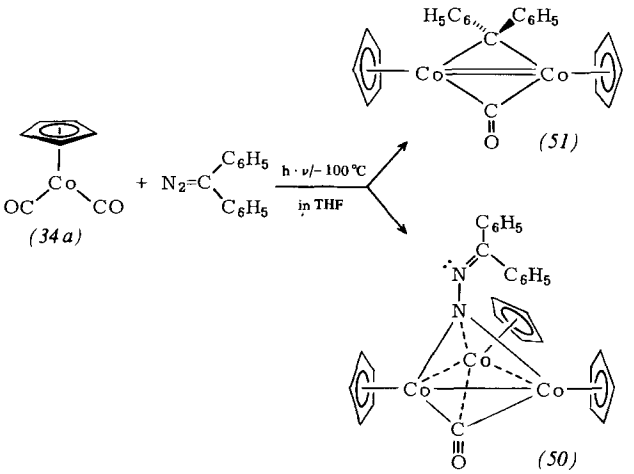


(48)



L = $P(C_6H_5)_3$ (49)

In general, however, we have to resort to indirect methods to produce mononuclear diazo complexes; such methods elaborate the complexed diazoalkane system from dinitrogen- or hydrazine complexes. Terminal polycoordination is a special case. It has repeatedly been encountered in the complex chemistry of diazoalkanes and leads to stabilization of cluster fragments: the photoreaction of $Fe(CO)_5$ with diphenyldiazomethane gives not only a dinuclear μ-hydrazido derivative but also a trinuclear organometallic hydrazone[78]. Similarly, diphenyldiazomethane has been introduced into the stable cluster molecule of *(50)* by low temperature photolysis with the cobalt compound *(34a)*; the μ-methylene complex *(51)* is formed at the same time. Hence this reaction provides



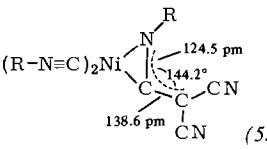
(34a) (51) (50)

the first example of simultaneous stabilization of a diazo compound and the corresponding carbene in a transition metal complex[79]. As in all other cases, the intact diazo molecule can be attached to the metal centers only under extremely mild conditions; thermal reaction gives only the nitrogen-free μ-methylene derivatives *(51)*[79].

Type II is frequently considered for primary adducts (organometal + diazoalkane); it has not yet been verified in stable compounds.

Type III has been achieved by ligand displacement reactions on some zerovalent metal complexes of the nickel group: under mild conditions (−78 to 0 °C) a ligand of "bis(*tert*-butyl isocyanide)nickel" and its palladium homolog, as well as other similar compounds, is replaced by 9-diazofluorene or diphenyldiazomethane[80], resulting in thermally labile diazoalkane derivatives of general composition $L_2M[N_2{=}CCR']$ [M = Ni, Pd; L = $(CH_3)_3C{-}N{\equiv}C$, $P(C_6H_5)_3$]. X-Ray structure analysis confirms the postulated geometry in the case of $[(CH_3)_3C{-}N{\equiv}C]_2Ni$(9-diazofluorene)[81]: the bent diazoalkane skeleton is bonded *unsymmetrically* by its two N atoms to the metal atom as a formally bidentate ligand.

In contrast, the action of dicyanodiazomethane on tetrakis(*tert*-butyl isocyanide)nickel at −10 °C in *n*-hexane solution leads not to the substitution product $[(CH_3)_3C{-}N{\equiv}C]_2Ni$(dicyanodiazomethane) but surprisingly to the ketenimine complex *(52)*—the overall result of addition of the carbene $:C(CN)_2$ to the isocyanide fragment $(CH_3)_3C{-}N{\equiv}C$[82,83].



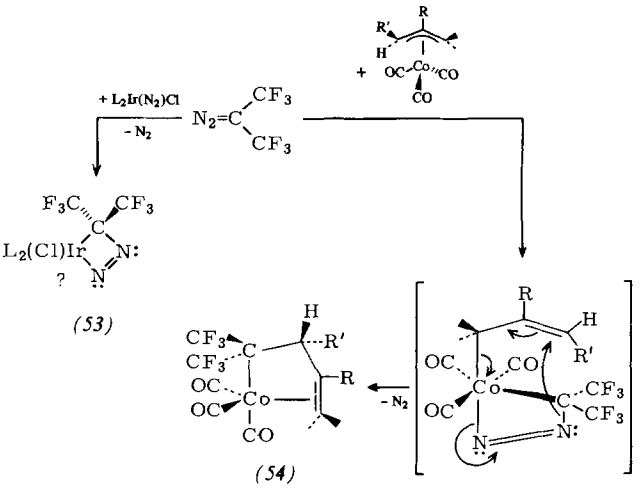
(52)

R = $(CH_3)_3C$

Apart from being the first example of a heterocumulene system RR'C=C=X [X = O, N—R] coordinated to the metal by way of its carbon—heteroatom bond, and not the C=C function as in all other species of this kind, compound *(52)* also warrants attention because it apparently also catalyzes formation of ketenimine from isocyanides and diazoalkanes.

No example of π(C=N) coordination as in *type IV* is known. The diazoalkane may be activated for a cleavage of the N=N bond, such as could be operative in the formation of ketimine complexes from diazoalkanes[84].

[1+3] Cycloadducts belong to *type V*. There are no unequivocal examples of this structural type. This kind of coordination was attributed to the product *(53)*, which is thought to possess a diazairidacyclobutene structure with a trigonal-bipyramidal central metal[85].



(53) (54)

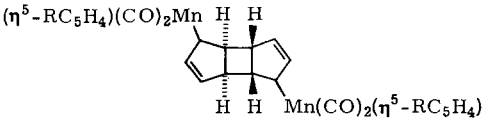
R, R' = H, CH_3; L = $P(C_6H_5)_3$

Cycloadducts of this kind are usually not resistant to decomposition by elimination of N_2: thus π-allyl(tricarbonyl)cobalt complexes are transformed by $(CF_3)_2C{=}N_2$ into the carbene addition products *(54)* with refunctionalization of the π-allyl systems. These reactions lead to 3-butenyl systems which are attached to the metal *via* the olefin function and also by alkyl-type bonding as bidentate chelate ligands. In view of the mild reaction conditions, attack by the free carbene on the metal is unlikely. Instead, 1 : 1 adducts are probably formed initially and then rearrange with loss of their four-membered ring structure to give the stable products *(54)*[86].

The behavior of the π-allyl—cobalt compounds also exemplifies the formation of complexed products from the diazoalkanes in the coordination sphere of a metal. A foreign ligand is not essential for the success of this reaction: formation of azine complexes on reaction of nickel, palladium, and platinum complexes with $(CF_3)_2C{=}N_2$ takes place under conditions in which no perfluoroacetone azine is formed from the diazo component[85, 87, 88]. An initial 1,3-dipolar addition of $(CF_3)_2C{=}N_2$ to the complex core L_2M is assumed to occur. Opening of the four-membered M—N—N—C heterocycle and attack of a further diazo molecule explains formation of the stable final product. The pronounced dipole character indeed appears to play a dominant role, for no well-defined metal complexes could be isolated with trimethylsilyldiazomethane[87, 88].

8. Organometallic Syntheses with Diazocyclopentadienes and Diazoindene

The successful synthesis of new carbene and methylene complexes from diazoalkanes called for studies on cyclic diazo compounds. This field appears all the more attractive because the complex stabilization of carbocyclic carbenes is still a topical problem of organometallic chemistry. Should it not be possible to synthesize cyclopentadienylidene complexes from diazocyclopentadienes? Only partial successes have hith-



(55), R = H, CH_3

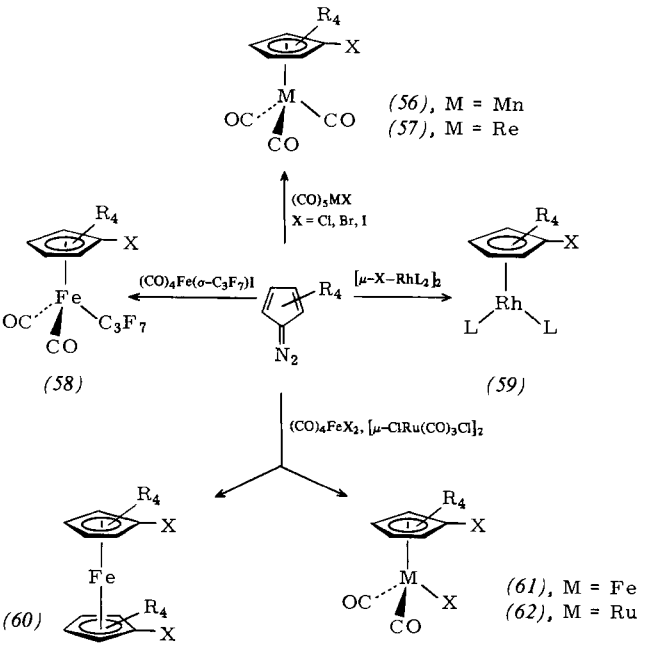
erto been reported: thus the action of the manganese complexes *(23)* on diazocyclopentadiene gave not the expected mononuclear cyclopentadienylidene complexes but instead their [2+2] cycloadducts *(55)*. A crystal structure analysis showed these products to contain a novel tricyclic $C_{10}H_8$ dicarbene bridge[89].

8.1. Halocyclopentadienyl and Haloindenyl Complexes

On use of carbonyl halides of manganese[90, 91, 93, 95], rhenium[94], iron[92, 96], ruthenium[97], and rhodium[91] as acceptors for cyclopentadienylidene or indenylidene, however, the aromatization tendency of the C_5 system could be exploited to open up a facile, productive synthesis of halogenated η^5-cyclopentadienyl and η^5-indenyl complexes.

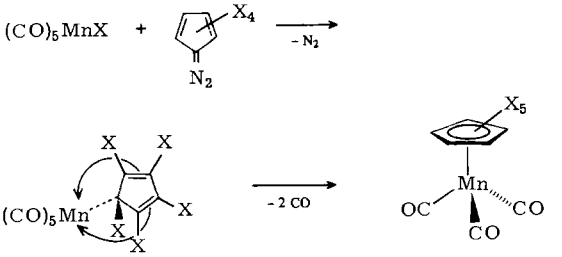
The starting materials are readily available in large quantities[6] and the yields all high or even quantitative. No alternative methods are available for most of the compounds of types *(56)—(62)* synthesized in this way.

The question of when the nitrogen is actually eliminated must remain unanswered. It has been established, however, that insertion of the intact diazo compound or the carbene derived therefrom into the metal—halogen bond takes place either *before* or *immediately after* elimination of N_2: if the reaction is performed without strong heating then not only the *pentahapto*-derivatives but also the *monohapto*-halocyclopentadienyl compounds can be isolated which still contain all five CO groups of the starting compound[90, 95]. It is particu-



R = H, C_6H_5, Cl, Br

larly interesting that on melting the η^1-complexes $(CO)_5Mn(\eta^1\text{-L})$ *(63)* undergo vigorous liberation of CO to give quantitative yields of the η^5-derivatives $(CO)_3Mn(\eta^5\text{-L})$ *(56)*, L = *e.g.* C_5Br_5[95]. This clearly shows that the diene-like η^1 ligand substitutes two CO ligands within the same molecule and aromatizes to the η^5 system. Although the η^1 intermediates have so far proved isolable in just a few cases, it seems reasonable to assume that most syntheses of this kind proceed *via* the η^1 compounds.



X = Cl, Br

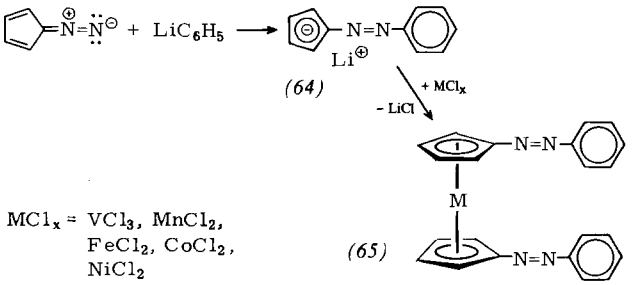
The dihalogen complexes $(CO)_4FeX_2$, X = Br, I, correspondingly lead not only to the mono-cyclopentadienylated products of type *(61)*, R = H, but also provide a means of synthesizing 1,1′-dihaloferrocenes *(60)* by consecutive transfer of cyclopentadienylidene. The reactivity of the $Fe(CO)_2X$ fragment determines the product pattern[96].

The diazo procedure for the synthesis of substituted π-cyclopentadienyl complexes differs fundamentally from all other methods in that all substituent positions are already fixed in the starting compounds; the halogen shift from the metal to the cyclopentadienyl unit occurs specifically to the original diazo carbon atom[98]. Thus, this synthetic procedure is characterized by a clear "building-block" principle. Apart from the synthesis of the *pentahapto* complexes, interest also attaches to the synthesis of novel *monohapto* derivatives of the C_5X_5

ligands which is dependent on the reaction conditions and product stability.

8.2. Sandwich-Type Phenylazocyclopentadienyl Complexes

At this point, it is fitting to recall an elegant synthesis of bis(η^5-phenylazocyclopentadienyl)metal complexes developed by *Pauson* and *Knox*[99-101]: the action of LiC_6H_5 on diazocyclopentadiene leads quantitatively to the diazotate *(64)* which affords the sandwich complexes *(65)* in very good yields with the corresponding anhydrous metal chlorides.



Compound *(64)* behaves in the same way as the unsubstituted cyclopentadienide ion. The manganese compound *(65)* undergoes the same reactions as $Mn(C_5H_5)_2$ with $FeCl_2$ and with H_2O [formation of $(C_6H_5—N=N\text{-}\eta^5\text{-}C_5H_4)_2Fe$ and $Mn(OH)_2$, respectively], and should therefore have a similar saltlike structure. The other compounds *(65)* resemble the unsubstituted sandwich complexes $(\eta^5\text{-}C_5H_5)_2M$ in their physical properties; their chemistry has hardly been studied.

8.3. Advantages of the Diazo Method

The development of an effective synthesis of halogenated cyclopentadienyl complexes closes a gap. Even the preparation of η^5-monohalocyclopentadienyl complexes was hitherto frequently possible only *via* tortuous routes involving numerous intermediates[102].

In contrast to the universally applicable reagents such as LiC_5H_5, NaC_5H_5, C_5H_5MgBr, TlC_5H_5, and cyclopentadiene used for preparing unsubstituted C_5H_5 complexes, the halogen derivatives $LiC_5H_{5-n}X_n$, $NaC_5H_{5-n}X_n$, $C_5H_{5-n}X_nMgBr$, $TlC_5H_{5-n}X_n$ are either unknown or thermolabile so that they decompose during the synthesis. Although perchlorocyclopentadiene is commercially available in kilogram quantities it is not suitable for preparing perchlorocyclopentadienyl complexes. The Tl, $P(C_4H_9)_4$, and $(C_2H_5)_3NH$ salts of the C_5Cl_5 anion decompose in solution above $-30°C$ and can only be stored below *ca.* $-15°C$ in the solid state.

The metalation/halogenation procedure is also a known method for the introduction of halogen into π-bonded cyclopentadienyl substituents; the best variants involve organomercury intermediates. This technique has proved of value for the preparation of simple halogen derivatives[103]. With regard to multiple substitutions, the method suffers from the poorly controllable formation of mixtures of isomers, whose components prove inseparable by conventional dissolution or crystallization operations or by sublimations as a result of almost identical solubilities and volatilities. Thin-layer chromatography gives satisfactory results on only rare occasions. Moreover, consecutive metalation/halogenation is only of limited applicability owing to the extremely low yields of perhalogenated cyclopentadienyl complexes. Thus, it is hardly surprising that decachloroferrocene and -ruthenocene[104] (yields $<5\%$) are still the only known perhalogenated C_5 sandwich complexes.

Seen against this background, the facile entry to perhalogenated cyclopentadienyl systems *via* diazo compounds is very welcome, particularly since it is known that strongly electron-withdrawing substituents greatly enhance resistance to oxidative processes[104]. These compounds also permit the first comparative studies on the reactivity of the metal—cyclopentadienyl bond as a function of the electron density in the ring and at the metal center.

9. Diazoalkane Reactions of Carbonyl Transition Metal Hydrides

Carbene insertion into metal-hydrogen bonds according to

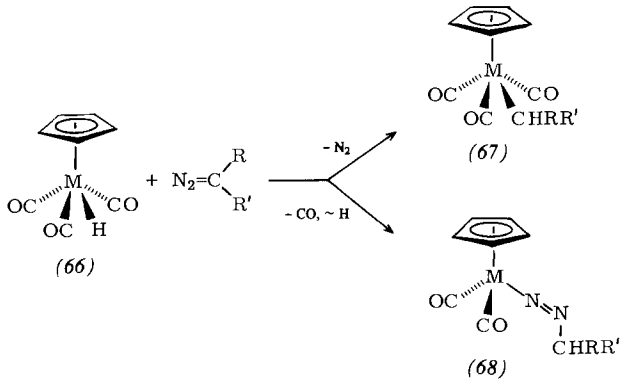
$$L_xM—H + CH_2N_2 \rightarrow L_xM—CH_3 + N_2$$

provides a simple route for the preparation of alkylmetal compounds[105-107]. In the chemistry of metal carbonyls, this reaction was first reported in 1955 when tricarbonyl(η^5-cyclopentadienyl)methylmolybdenum[108] and -tungsten[109,110] were synthesized from the hydrides with diazomethane as the first stable alkyl(carbonyl)transition metal compounds; tricarbonyl(η^5-cyclopentadienyl)ethyltungsten could be obtained from $(\eta^5\text{-}C_5H_5)W(CO)_3H$ and diazoethane[110]. Under special reaction conditions, $(CO)_5MnH$ can be transformed into $(CO)_5MnCH_3$ in analogous manner[111,112]. In contrast, bis(η^5-cyclopentadienyl)hydridorhenium does not react with diazomethane[113]. While no reports have been published about attempted methylene insertion into tetracarbonyl(hydrido)cobalt, the analogous compound $HCo(PF_3)_4$ reacts at $-50°C$ with diazomethane to give initially the isolable oxonium complex $[(C_2H_5)_2OCH_3]^+[Co(PF_3)_4]^-$ which above $0°C$ undergoes 94% conversion into the methyl derivative $CH_3Co(PF_3)_4$ and 6% conversion into the ethyl derivative $C_2H_5Co(PF_3)_4$[114]; the latter admittedly liberates ethylene under mild conditions to regenerate the hydride[115], and yet its formation *via* the oxonium salt draws attention to an interesting mechanistic aspect of the reaction of strongly acidic transition metal hydrides with simple diazoalkanes[51].

As a whole, the preparative applications of metal hydride alkylation with aliphatic diazo compounds seem to be subject to limitations arising mainly from the extent of organometal-catalyzed decomposition of diazoalkanes, especially since carbonyl hydrides are generally acidic in nature.

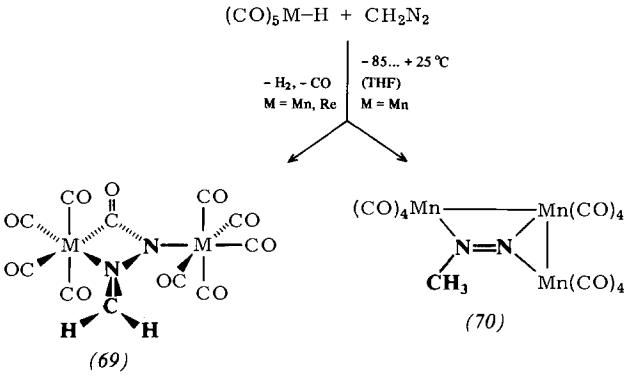
A recent comparative study on the model system *(66)* has shown that the interaction between diazoalkanes and carbonylmetal hydrides is far more complex than previously assumed[117-119]. Insertion of alkylidene to form the alkyl complexes *(67)* usually contributes little to the overall reaction. The nitrogenous derivatives *(68)*, containing the *C*-protonated diazoalkanes as monodentate three-electron ligands, then predominate among the products. These reactions, involving carbonyl substitution and 1,4-hydrogen shift, permitted the elegant preparation of the hitherto unknown *alkylazo* complexes. Crystal structure analysis performed on the

complex *(68)*, M=W, R=R'=H, confirmed the proposed geometry and shows the N—N bond (122 pm) to have double bond character[120].



M = Mo, W; R, R' = H, CH_3, $Si(CH_3)_3$, C_6H_5

Formation of nitrogenous products takes precedence over CH_2 insertion with other simple carbonyl hydrides too: even at −80 °C the weak acid $(CO)_5MnH$ reacts with diazomethane in tetrahydrofuran, liberating CO and H_2 but not N_2. The intact diazo molecule and the methylazo group derived therefrom, respectively, are incorporated in the products *(69)*, M=Mn, and *(70)*, which are isolable at room temperature. No fragmentation of the acid-labile diazo substrate has taken place[122,123]. The less reactive homolog $(CO)_5ReH$ behaves in essentially the same way[121].



The reactions leading to the cyclic complexes *(69)* and *(70)* are the first examples of coordination of diazomethane to metal centers *via both* nitrogen atoms. The formation of these complexes underlines the fact that the basicity of the carbon atom does not necessarily determine the reactions of diazomethane with metal compounds. The primary reaction steps may occur exclusively at the diazo function, provided that the organometallic components fulfill the necessary structural conditions. The preparation of μ_3-$CH_3N_2[Mn(CO)_4]_3$ *(70)* once more demonstrates the utility of diazomethane for the synthesis of alkylazo complexes. These compounds are currently being studied, both from a structural viewpoint and with regard to their relevance to problems of nitrogen fixation[124].

10. Closing Remarks

What have we learned in the foregoing discussion? Firstly, diazoalkanes are versatile reagents for the formation of numerous ligand systems on transition metal substrates. The complexes hitherto synthesized from aliphatic diazo compounds belong to the following classes: 1) *Nitrogen-free compounds:* alkyl, olefin, acetylene, carbene, μ-methylene, η^2-ketene, μ-methylidyne complexes, carbene adducts (metallacycles), σ- and π-halocyclopentadienyl- as well as π-(1-haloindenyl) complexes, and halogenated sandwich complexes of the ferrocene type. 2) *Nitrogenous compounds:* dinitrogen complexes, σ- and π-coordinated diazoalkane derivatives, alkylazo, carbene chelate, ketenimine, ketimine, ketazine, and imino amide complexes.

Secondly, it has also been found that the reactions of organometallic compounds with diazoalkanes display a pronounced structural dependence. The syntheses of π-halocyclopentadienyl- and π-haloindenyl complexes of the cymantrene[*] type starting from diazocyclopentadiene and its derivatives and from diazoindene, respectively, can hardly be improved upon as regards simplicity and yield. The σ-halocyclopentadienyl intermediates can be isolated. Repetitive cyclopentadienylation also provides a route to halogenated sandwich compounds. Acyclic diazo compounds preferentially afford carbene or μ-methylene complexes; however, if the metal substrates contain metal—hydride or metal—halogen functions susceptible to carbene insertion, then formation of alkyl- and/or alkylazo complexes will predominate. The production of cyclic carbene addition products is dependent upon the presence of additional basic centers in the diazo component. Thus diazomalonic ester derivatives undergo [2+3]-carbene addition to give five-membered metallacyclic compounds. Complexed carbynes are expected on use of α-mercurated diazoalkanes. In some isolated cases, unfragmented diazo molecules can be attached to transition metal centers. With few exceptions, the 1:1 adducts are rather unstable, in keeping with their main role as primary products.

The wealth of products obtained from the entire area of organometallic complex chemistry can still not disguise our rather crude knowledge of the relevant reaction mechanisms. Many questions await elucidation, which is probably rendered all the more difficult by the frequent superposition of somewhat unpredictable catalytic processes on the stoichiometric reactions. The future of organometallic diazoalkane chemistry therefore lies not only in promising preparative advancements but also in detailed mechanistic studies.

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[*] "Cymantrene" has the formula $(\eta^5\text{-}C_5H_5)Mn(CO)_3$.

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Electrostatics, the Chemical Bond and Molecular Stability

By Sidney W. Benson[*]

Electrostatic models of the chemical bond are based on the Virial Theorem and hold promise for providing a reliable and accurate method for predicting heats of formation of molecules and free radicals. The Principle of Alternating Polarity which states that those compounds are most stable in which atoms of opposite polarity are bonded is shown to be quantitatively described by electrostatic models. Current fixed partial-charge models account for ΔH_f^0 of hydrocarbon molecules and radicals. With inclusion of polarization effects, whose energies are small, they also account for the dipole moments in hydrocarbons. A brief account is given of a more general model with significant polarization interaction which is under development and which appears to be able to account for both ΔH_f^0 and dipole moments of polar molecules.

1. Introduction

One of the major goals of theoretical chemistry is to be able to predict equilibrium constants (states) for all possible stoichiometric reactions given composition, volume, solvent, and temperature. To do this requires a knowledge of the heats of formation, entropies and heat capacities of both reactants and products. This is a necessary first step before the broader goal of predicting rates of approach to these equilibrium states can be achieved. An *ab initio* quantum mechanical approach to such a task is not feasible now or in the near future. Empirical quantum approaches have been numerous and more or less encouraging but none of them have demonstrated the required accuracy in ΔH_f^0 (<1 kcal/mol).

An alternative approach which is also empirical, is to try to generalize from known observations on data using physical laws as a guide. This has been very fruitful, culminating in

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a hierarchy of Additivity Laws for molecular properties[1] which are capable of reproducing most data on ΔH_f^0, S^0, and Cp^0 to within the experimental uncertainties. The level at which such accuracy is attained is called the "Law of Additivity of Group Properties". It suffers from at least two deficiencies. The first of these is the requirement of an extensive data base to establish the empirical numbers. A group is defined as a polyvalent atom together with all of its ligands. A typical example would be the methyl group in hydrocarbons, designated by $C—(H)_3(C)$. Since saturated carbon is tetravalent with four ligands there are about 10^4 possible groups centered on carbon if we consider carbon itself and only nine other elements as possible ligands. Trivalent elements such as nitrogen would have 10^3 groups and so on. In practical terms there are not available 10^4 pieces of accurate data on the ΔH_f^0 of chemical compounds from which to provide such a data base.

The second deficiency has to do with the fact that for very polar compounds (*i.e.*, those containing two or more substituents such as F, CN, OH, NO_2, *etc.*) deviations from group additivity can be in excess of 6 kcal/mol. Also, very highly branched compounds with "strained" configurations require extra-group corrections in order to reproduce known values of ΔH_f^0. However, a number of simple and not-so-simple empirical schemes exist for making strain corrections[2,3] to group additivity estimates of ΔH_f^0 so that strain is not as severe a problem as polarity.

These latter problems with group additivity arising from polar and steric interactions are not serious since it is reasonable to anticipate correction schemes to account for such effects. However, the data base requirements do seem prohibitive and so it is tempting to consider alternative approaches. Of the alternatives, the most attractive is the Law of Bond Additivity. The premise of bond additivity which has historic foundations[4,5] is that molecular properties may be considered to be additive in contributions from the bonds comprising the molecule. Since with only about 40 atoms of common chemical interest forming covalent compounds there are at most 800 bonds, the data requirements seem almost modest. For the most commonly occurring 15 atoms only 120 single bonds, 66 double bonds, and 21 triple bonds can exist and it is possible to envision a complete scheme of empirical thermochemistry from existing or readily available data.

An inspection of bond additivity applied to $\Delta H_{f\,298}^0$ data[4] indicates that maximum deviations from an optimized scheme are about 12 kcal/mol for very polar or sterically strained compounds while average deviations are in the range of 4 kcal/mol. Since, as we shall shortly see, these deviations are not random but seem to be systematic with types of substituents in homologous series, it raises the prospect of finding simple empirical schemes for estimating them in the manner suggested by *Zahn*[6] and by *Allen*[7].

2. Theoretical Basis—The Virial Theorem

The Schrödinger Equation for an n-body system obeys the Virial Equation, which states that the total average kinetic energy T of the system is precisely equal to $-\frac{1}{2}$ the total coulombic energy of all the particles, E_c:

$$T = -\tfrac{1}{2} E_c \tag{1}$$

Note that for a stable bound system, E_c is negative and corresponds to the energy required to separate the particles infinitely far from each other with zero final kinetic energy. Hence the binding or total energy of the system E_B which is $T+E_c$ (neglecting small spin interactions) is precisely $\frac{1}{2}E_c$. The total coulombic energy of such a system can then be written as:

$$E_c = \tfrac{1}{2}\sum\sum' \frac{Z_i Z_j}{r_{ij}} + \sum Z_i \int \cdots \int \frac{P_k(\tau_k)\,d\tau_k}{r_{ik}} + \tfrac{1}{2}\int \cdots \int_{n\neq m} \frac{P_n(\tau_n)\,P_m(\tau_m)}{r_{nm}}\,d\tau_m\,d\tau_n \tag{2}$$

where Z refers to nuclear charges and P to electronic charge densities. If we had some prior knowledge of these charge density distributions we would not need to solve the Schrödinger equation to calculate E_c. In the event that the charge density distributions could be written as sums of products of one-electron wave functions the integrations would be straightforward. If on the other hand important correlation effects proscribed such a simplified form for the charge density the integration might be quite complex or indeed impossible.

Microwave and infrared spectroscopy together with modern electron diffraction studies have given us fairly accurate data (± 0.01 Å or better) on the positions of the nuclei in molecules. (Note that the mean amplitudes of nuclear motion of neighboring atoms amount to relative displacements of about ± 0.05 Å.) Thus, if we are willing to accept the empirical details of molecular structures our problem reduces to guessing the electronic density distributions. However, we can extend our empiricism one step further by adopting as a starting point the hypothesis that charge density distributions in localized bonds do not change greatly when one changes neighboring bonds in a molecule. This would be consistent with the Law of Bond Additivity for which deviations, as noted, are usually in the range of ± 4 kcal/mol and seldom reach ± 12 kcal/mol. When we consider that ionization potentials of molecules are in the range 8—15 eV (184—345 kcal/mol) these deviations are indeed very small perturbations of the electron binding energies.

A further empirical support for the hypothesis that bonds are only slightly affected by neighboring substituents is the observation that bond lengths change very little from compound to compound. Thus C—H bonds in alkanes vary very little from a mean value of 1.09 ± 0.01 Å. Even on progessing from C_2H_6 to C_2H_4 to C_2H_2 the decrease in C—H bond length is only about 0.03 Å. The same appears to be true even for very polar bonds such as C—F or C—O, with the result that one can talk of average bond lengths with some confidence. On the other hand, in unsaturated systems where delocalization of electron motions becomes significant we can find larger and more systematic variations in bond lengths. Thus C—C bond lengths can vary from 1.54 ± 0.01 Å in alkanes to 1.46 Å in butadienes, still however only a 5% change[10].

One final observation on the stiffness of bonds is appropriate. Most single bonds have stretching force constants in the range of 5×10^5 dynes/cm. Such a force constant would require an energy of 0.3 kcal/mol to stretch or compress a bond by ± 0.03 Å from its normal length[8]. Since the latter

value circumscribes variations in single bonds in saturated molecules one concludes that the larger variations in binding energies of molecules which are observed must come from interactions other than those arising from changes in bond lengths. Let us consider an actual example. In the endothermic disproportionation reaction[9]

$$CH_4+CF_4 \rightleftharpoons 2CH_2F_2 \quad \Delta H_r^0 = +12\pm3\,\text{kcal/mol}$$

the total number of C—H and C—F bonds are conserved. If bond additivity held, ΔH_r^0 would be zero. The variations in C—F and C—H bond lengths in the above compounds are less than 0.05 Å[10] which would correspond to energy changes far less than the observed heat of reaction. The implication of such observations is that the volume occupied by bonding electrons in a given single bond acts like an incompressible fluid and tends to be conserved in chemical reactions. This further implies that the energy changes in such disproportionation reactions must arise from changes in coulombic interactions involving the electrons of non-bonded atoms.

3. The Electrostatic Model—Hydrocarbons

Atoms in their ground electronic states are electrically neutral and have no dipole moments. A stable diatomic species can be formed between two such atoms only if their interaction distorts their valence shells. The simplest such distortion is to produce a dipole, and single covalent bonds may be looked upon as arising from the interaction of two such dipoles[11]. The valence electrons in the bond must have correlated motions or the dipolar interaction would average to zero. Homonuclear bonds must have identical dipolar distortions. In heteronuclear bonds this is not the case and when the bonded atoms differ enough in their electronegativity we have the case of ionic bonding[12].

The first electrostatic model to successfully correlate bond energies in diatomic molecules was proposed by *Pauling*[12]. He assigned a constant electronegativity to each atom which allowed the estimation of heteronuclear single bond energies from observed homonuclear bond energies. It was not clear how to extend this scheme to polyatomic molecules and a number of efforts have been made[13,14]. *Sanderson*'s[14] is the most comprehensive but it lacks the precision to be of quantitative utility.

The electrostatic model for polyatomic systems designed by the author[15] while less comprehensive than *Sanderson*'s is also simpler. It starts with a description of the valence electrons around each atom in a bond in terms of a deficiency (or excess) similar to the ionicity suggested by *Pauling*. In a homonuclear bond such as C—C or H—H the ionicity is zero. However, in a bond such as C—H or Si—H we may expect some net transfer, ε, of electronic charge from one atom to the other and this gives an electrostatic character to each bond. If we reference heteronuclear bonds to homonuclear standard bonds where such electron transfer does not exist, then we can define an electrostatic energy:

$$E_{el} = -\frac{\varepsilon^2}{r} \tag{3}$$

where r is the bond length across which the electronic charge ε has moved. E_{el}, which is always negative, is a measure of the extra stability of the heteronuclear bond compared to the homonuclear bonds. If, however, we are concerned with the interaction between bonds as in the present case, then this extra self-energy of a bond is not of any real interest to us. Instead the model gives us a method for estimating the interaction between adjacent bonds located on a central atom and, as we shall see, next nearest neighbors as well.

Let us consider a simple example of a divalent species X which may be an atom such as S or O or a grouping of atoms centered as one polyvalent atom such as CH_2 or NH and two different ligands A and B. We can have three different molecules from these species XA_2, XB_2, and the unsymmetrical XAB. From the standpoint of bond additivity we are interested in the heat of the reaction:

$$XA_2 + XB_2 \rightleftharpoons 2XAB \tag{4}$$

The heat of this reaction represents the difference in interaction of the bonds X—A and X—B with each other minus the self-interactions X—A/X—A and X—B/X—B. As we have already remarked, changes in geometry are slight in such reactions and the electrostatic model assigns the bond interactions to the electrostatic interaction which can now occur between the non-bonded atoms. Figure 1 illustrates the case in which A and B bear partial charges $-a$ and $-b$ respectively, and, to preserve molecular neutrality, X must bear the opposite charges as shown.

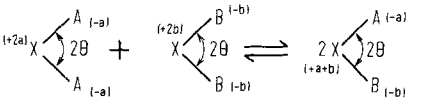


Fig. 1. Electrostatic energy in a simple disproportionation reaction [Eq. (5) and (6)].

$$\Delta E_{el} = 2E_{el}(XAB) - E_{el}(XA) - E_{el}(XB_2)$$

$$= \left(\frac{-2a^2}{r_{XA}} - \frac{2b^2}{r_{XB}} - \frac{2ab}{r_{XA}} - \frac{2ab}{r_{XB}} + \frac{2ab}{r_{AB}}\right) + \left(\frac{4a^2}{r_{XA}} - \frac{a^2}{r_{AA}}\right) + \left(\frac{4b^2}{r_{XB}} - \frac{b^2}{r_{BB}}\right) \tag{5}$$

$$= \frac{2a^2}{r_{XA}} + \frac{2b^2}{r_{XB}} - 2ab\left[\frac{1}{r_{XA}} + \frac{1}{r_{XB}}\right] - \left[\frac{a^2}{r_{AA}} + \frac{b^2}{r_{BB}} - \frac{2ab}{r_{AB}}\right] \tag{6}$$

If bond distances and angles are approximately conserved then it can be shown that the first three terms on the right-hand side of Equation (6) for ΔE_{el} are positive and the last bracketed term in this equation is similarly positive. But it will be noted that the former terms are individually about twice or more as large as the corresponding terms in brackets so that they dominate the value of ΔE_{el}, which is then positive.

When $a=b$ and $r_{XA}=r_{XB}$ then $\Delta E_{el}=0$. When a and b are of opposite sign $\Delta E_{el}>0$. When $r_{XA}\sim r_{XB}$ then ΔE_{el} is given by:

$$\Delta E_{el}(r_{XA} \cong r_{XB}) \approx \frac{2(a-b)^2}{r_{XA}} - \frac{(a-b)^2}{r_{AA}} > 0 \tag{7}$$

since $r_{AA}=2r_{XA}\sin\theta$.

Thus it appears that the disproportionation of symmetrical species to produce unsymmetrical species should in general be endothermic and in fact we find this to be a fairly good rule. Some examples are provided in Table 1, selected for elements of groups 4, 5, 6, and 7. Some exceptions to the general rule are also noted and we shall comment on these later. Note also that the heats of disproportionation tend to be small and usually below 6 kcal/mol in absolute value.

Table 1. Some heats of disproportionation ΔH_r^0 of symmetrical species: $A_2X + B_2X \rightleftharpoons 2ABX$

Reaction	ΔH_r^0 [kcal/mol]	Ref.
$H_2O + Me_2O \rightarrow 2MeOH$	6.0	[15]
$H_2O + F_2O \rightarrow 2HOF$	5 ± 3	[1]
$H_2O + Cl_2O \rightarrow 2HOCl$	1 ± 1	[1, 16]
$H_2S + Me_2S \rightarrow 2MeHS$	2.8	[5]
$H_2S + (HS)_2S \rightarrow 2HSSH$	4.4	[5]
$H_2NH + Me_2NH \rightleftarrows 2MeNH_2$	4.5	[5]
$Me_2NMe + H_2NMe \rightleftarrows 2HNMe_2$	2.4	[5]
$H_2CH_2 + Me_2CH_2 \rightleftarrows 2MeCH_3$	2.5	[5]
$H_2CF_2 + F_2CF_2 \rightleftarrows 2HCF_3$	0 ± 2	[5]
$H_2CH_2 + F_2CH_2 \leftrightarrows 2H_3CF$	12 ± 2	[5]
$H_2CH_2 + Cl_2CH_2 \leftrightarrows 2ClCH_3$	1.5 ± 1.4	[5]
$Cl_2CH_2 + Cl_2CCl_2 \leftrightarrows 2HCCl_3$	-2.7 ± 1	[5]
$H_2CH_2 + I_2CH_2 \leftrightarrows 2ICH_3$	-4.4	[1]
$H_2C{=}CH_2 + Me_2C{=}CH_2 \rightleftarrows 2HMeC{=}CH_2$	1.3	[5]
$H_2C{=}CF_2 + F_2C{=}CF_2 \rightarrow 2HFC{=}CF_2$	4.5 ± 4	[5]
$H_2C{=}CCl_2 + Cl_2C{=}CCl_2 \rightarrow 2HClC{=}CCl_2$	-2 ± 4	[5]
$H_2CO + Me_2CO \rightarrow 2HMeCO$	-1.7 ± 1.5	[1]
$Cl_2CO + Me_2CO \rightarrow 2ClMeCO$	-13.5	[1]
$Me_2Hg + Cl_2Hg \rightarrow 2MeHgCl$	-12 ± 3	[1, 15]

We find much larger values for heats of disproportionation when we consider compounds with one or more π bonds. This is illustrated for a few cases in Table 2. Again the values of ΔH_r^0 are all positive and far in excess of anything attributable to changes in bond lengths.

Table 2. Some heats of disproportionation of compounds with one or more π bonds.

Reaction	ΔH_r^0 [kcal/mol]	Ref.
$CO_2 + CS_2 \rightarrow 2COS$	0	[17]
$CO_2 + CH_2{=}C{=}CH_2 \rightarrow 2CH_2{=}C{=}O$	27 ± 2	[1]
$CO_2 + H_2CH_2 \rightarrow 2CH_2CO$	60 ± 2	[1]
$CS_2 + H_2CH_2 \rightarrow 2CH_2CS$	30 ± 4	[17]
$CO_2 + CCl_4 \rightarrow 2COCl_2$	12	[1]
$CO_2 + CF_4 \rightarrow 2COF_2$	14 ± 4	[1]

This simplest model of a fixed electrostatic interaction between non-bonded atoms assigns equal and opposite partial charges δ_{XY} to each atom X and Y connected by a bond. Such a model is useful when δ_{XY} is a transferable constant independently of whatever other atoms may be bonded to X and Y. The test of such a model is that it reproduces the thermal data on heats of reaction using the principle of bond additivity plus the electrostatic energy representing the non-bonded interactions. This behavior has been demonstrated in the case of the simple hydrocarbons, namely the alkanes[18] branched or unbranched, simple olefins, acetylenes and aromatics[19] and finally for the alkyl free radicals[20]. Using a charge ε_i of $+0.278 \times 10^{-10}$ esu on H and -0.278×10^{-10} esu on C in the aliphatic C—H bond it is possible to reproduce ΔH_f^0 (kcal/mol) of all the unbranched and singly branched paraffin hydrocarbon with the simple formula:

$$\Delta H_f^0(C_nH_{2n+2})_{gas} = -2.0(n+1) - 0.5 + E_{el} \quad (8)$$

where E_{el} is the sum of all of the electrostatic interactions in the paraffin:

$$E_{el} = \tfrac{1}{2} \sum_i \sum_j{}' \frac{E_i E_j}{r_{ij}} \quad (9)$$

In such a summation it is of sufficient accuracy (≤ 0.1 kcal) to represent all C—C bonds and C—H bonds each by standard lengths 1.54 Å and 1.09 Å respectively and take all angles as tetrahedral. Since the C—C bond is by symmetry, unpolarized, each group CH_3, CH_2, or CH in a hydrocarbon has an excess counter charge on the carbon atom equal to $-0.278k \times 10^{-10}$ esu, where k = the number of H atoms on that C-atom. Each such group then behaves as an electric dipole and its electrostatic interaction with neighboring CH_k groups is small (≤ 0.6 kcal) and falls off rapidly with distance[18].

A similar model works well for olefins, acetylenes, aromatics and free radicals with appropriate assignments of bond energies and charges to each bond. Table 3 summarizes the values used to reproduce the heats of formation for these compounds. With appropriate small corrections for non-bonded steric repulsions arising from *cis* and *gauche* interactions of CH_3 groups the electrostatic model is able to reproduce the $\Delta H_{f\,298}^0$ of the saturated and unsaturated hydrocarbons and alkyl free radicals to within the uncertainties in the data[21].

Table 3. Bond energies and partial charges used for reproducing the heats of formation $\Delta H_{f\,298}$ of hydrocarbons and alkyl radicals at 298 K.—For olefins and aromatics, a 1.0 kcal/mol repulsion is assigned to *cis*- or *ortho*-alkyl groups and 0.3 kcal/mol repulsion to geminal alkyl groups in olefins. For large, highly-branched alkanes 0.7 kcal/mol is assigned to *gauche* interactions and 1.5 kcal/mol to 1,5 methyl interaction (Ref. [1], page 30).

Bond	Energy [b] [kcal/mol]	Partial charge [c] [10^{-10} esu]
C—C	0.25	0
H—H	0	0
C—H	−1.13	0.278(H)
C_d—H	−3.3	0.32(H)
C_B—H	−2.2	0.32(H)
C_t—H	−5.2	0.36(H)
C•—H	11.9	0.12(H)
C_d—C	−5.5	0.12(C)
C_t—C	−8.0	0.16(C)
C_B—C	−2.0	0.12(C)
C•—C	14.0	0.04(C•)
C=C	0.25	0
C_B—C_B	6.5	0
C_d=C_d	34.0	0
C_t≡C_t	67.7	0

[a] The subscripts B, d, t signify benzene, doubly bonded, and triply bonded C-atoms.
[b] These are contributions to $\Delta H_{f\,298}^0$ for each bond.
[c] The strongest positive atom is given.

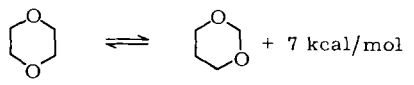
It is possible to make a similar analysis of organosilicon compounds with similar results[22]. Unfortunately the ΔH_f^0 data are of poorer quality for the silicon compounds and what there is shows such small deviations from bond additivity

that they are not very sensitive to the partial charge assignments.

That the hydrocarbons fit so well a simple model of non-bonded interactions is very likely fortuitous. First the charges involved are on the whole small. Aside from CH_4 itself the maximum partial charge on any atom is that in the CH_3 group where C carries a negative charge of 0.84×10^{-10} esu or about $^1/_6$ of an electronic charge. One consequence of this is that charge-induced charge-dipole interactions turn out to be quite small with energies of the order of less than 0.2 kcal/mol. As we shall see when we consider more polar molecules, net charges become appreciably larger and induction effects are no longer small enough to ignore.

4. The Principle of Alternating Polarity—Polar Molecules

The literature of organic chemistry has, for almost a century, been threaded by qualitative observations to the effect that those compounds are most stable in which elements of alternate polarity are joined to each other. In the case of polar substituents on aromatic nuclei it is known that *ortho* substitution is less stable than *meta* or *para* substitution. Thus *ortho*-dichlorobenzene is less stable than the *meta*- or *para*-isomers by some 2.5 kcal/mol, while *ortho*-difluorobenzene is similarly less stable by about 5 kcal/mol[5]. Larger effects are seen on comparing 1,3- and 1,4-dioxane. The 1,3-isomer is more stable by 7.0 kcal/mol, reflecting presumably the attractive configuration of two O-atoms attached to the same C-atom.



The electrostatic model of non-bonded interactions gives a simple and direct explanation for such observations and permits us to explore them in more quantitative fashion. In the simple example illustrated in Figure 1, the disproportionation of XA_2 with XB_2 is always endothermic when A and B are of opposite polarities (*a* and *b* of opposite signs) and no deviations from this example are known. However, when we try to apply this simple model to very polar species such as the halogens we find gross discrepancies.

These seem to have their origins in two sources. With very electronegative elements such as O and F, the partial charges are no longer small, as they were in the case of the hydrocarbons, and charge-induced charge-dipole effects can no longer be neglected. In addition the partial charges that are needed to account for changes in $\Delta H^0_{f\,298}$ of mono-substituted compounds (*e.g.* MeX and *t*-BuX) are much too small to account for the observed dipole moments of these compounds.

What one is required to do to account for the properties of the very polar molecules is to make an assignment of partial charges to each atom in the bond and in addition an assignment of a fixed dipole moment to the lone pairs on the electronegative atom. In polysubstituted compounds one also has to make explicit account of polarization effects and the energies of such interactions. As a consequence the model requires additional parameters and the calculations are more complex. At the moment only an approximate resolution has been made by the author and so the account given here will be restricted to reviewing some of the data and reporting the early results on a necessarily tentative model.

Table 4. Heats of formation of fluorinated methanes of the type CH_nF_{4-n} [18].

Compound	$-\Delta H^0_{f\,298}$ [kcal/mol]	$\Delta(-\Delta H^0_{f\,298})$	$\Delta^2(\Delta H^0_{f\,298})$
CH_4	17.9		
CH_3F	56.8 ± 2	39 ± 2	
CH_2F_2	108 ± 1	51 ± 2.3	12 ± 4.1
CHF_3	166 ± 1	58 ± 1.4	7 ± 3.0
CF_4	223 ± 1	57 ± 1.4	−1 ± 2.5

A relatively simple way to explore the magnitudes of non-bonded interactions is to examine the changes in ΔH^0_f in simple, homologous series where one group or atom replaces another. Table 4 shows the data for the series CH_nF_{4-n}. If bond additivity held, then the differences in heats of formation on replacing a C—H by a C—F bond would be constant. We see that on the contrary there is a large increase in stability of about 12 kcal/mol in going from CH_3F to CH_2F_2, above and beyond simple additivity. We can express this in terms of the disproportionation reaction:

$$2CH_3F \rightleftharpoons CH_4 + CH_2F_2 + 12 \text{ kcal/mol}$$

The first differences in $\Delta H^0_{f\,298}$, expressed as $\Delta(-\Delta H^0_{f\,298})$ increase to a maximum at CHF_3 and then decrease slightly. If non-bonded interactions could be treated as pairwise additive as is suggested in the simple electrostatic model, then the second differences $\Delta^2(\Delta H^0_f)$ would be constant[23]. The fact that they are not tells us that non-linear interactions must exist. The magnitude of such interactions is represented by the third order differences of about 6 kcal/mol for the fluorinated methanes. We find a similar, albeit smaller, effect in the series of chlorinated methanes shown in Table 5. Here, the first order differences are small and not too much larger than the experimental uncertainty. The second order differences are also small but the reversal of sign is unmistakable, again suggesting significant non-linear interactions between bonds.

Table 5. Heats of formation of the chlorinated methanes CH_nCl_{4-n} [1].

Compound	$-\Delta H^0_{f\,298}$ [kcal/mol]	$\Delta(-\Delta H^0_{f\,298})$	$\Delta^2(-\Delta H^0_{f\,298})$
CH_4	17.9		
CH_3Cl	19.6	1.7 ± 1	
CH_2Cl_2	22.8	3.2 ± 1	1.5 ± 1.4
$CHCl_3$	24.2	1.4 ± 1	−1.8 ± 1.4
CCl_4	22.9	−1.3 ± 0.5	−2.7 ± 1.2

In agreement with these trends in the chlorinated and fluorinated methanes is the comparable data on mixed chloro-fluoro-substituted methanes, CF_nCl_{4-n} shown in Table 6. We note that parallel to the CH_nF_{4-n} data (Table 4), the consecutive substitution of F for Cl leads to increasing stability (more negative ΔH^0_f) with values of the $\Delta(\Delta H^0_f)$ almost equal in absolute magnitude in the two sequences.

Table 6. Heats for formation of the compounds CCl_nF_{4-n} (data from Ref. [5]). Note that a change in ΔH^0_{f298} (CCl_3F) to −66.4 kcal/mol and of ΔH^0_{f298}(CCl_2F_2) to −114.0 kcal/mol would bring all the Δ^2 differences to about the same value of 4.4.

Compound	$-\Delta H^0_{f298}$ [kcal/mol]	$\Delta(-\Delta H^0_{f298})$	$\Delta^2(\Delta H^0_{f298})$
CCl_4	22.9		
CCl_3F	64±2	41±2	
CCl_2F_2	114.8±1.3	51±2.4	10±4.2
$CClF_3$	166.2±1.4	51.4±2	0±3.5
CF_4	223±1	57±1.5	5.5±3.5

Questions have always been raised concerning the reliability of the heat of combustion data on the fluorine compounds and it is of interest to note that what data do exist on oxygenated compounds show an almost identical trend[17]. Table 7 compares such data for some hydroxy-substituted methanes.

Table 7. Heats of formation of some hydroxy-substituted methanes $CH_n(OH)_{4-n}$ (data from Ref. [5] and Ref. [1]).

Compound	$-\Delta H^0_{f298}$ [kcal/mol]	$\Delta(-\Delta H^0_{f298})$	$\Delta^2(-\Delta H^0_{f298})$
CH_4	17.9		
CH_3OH	48.0	30.1	
$CH_2(OH)_2$	93±1	45±1	15±1.5

The second order differences are in surprising agreement with the corresponding fluorine compounds of Table 4. This, together with other such parallels, suggest that we could be quite confident in assigning a value of 7±2.6 kcal/mol to the ΔH^0_r of:

$$CH(OH)_3 + CH_3OH \rightleftharpoons CH_2(OH)_2 - 7\,\text{kcal/mol}$$

and hence a value of $\Delta H^0_{f298}[CH(OH)_3]_{gas} = -141 \pm 2$ kcal/mol. This allows us to predict that HCOOH is unstable with respect to hydration by 7 kcal/mol.

$$HCOOH(g) + HOH(g) \rightleftharpoons HC(OH)_3(g) - 7\,\text{kcal/mol}$$

It would further suggest that ΔH^0_{f298} of monofluorinated and difluorinated saturated hydrocarbons will be about 8±1 kcal and 16±1.5 kcal/mol more stable respectively than their hydroxy analogues.

An especially striking illustration of the principle of alternating polarity is seen on examining the effect of electronegative substitution on polyvalent electronegative elements. The substitution of F or OH for H in hydrocarbons leads to a more stable compound. The reverse turns out to be the case when the substitution takes place on an electronegative element. This is seen in Tables 8 and 9 where we examine the replacement in H_2O of H by F and OH respectively. In both cases we see that HOF and H_2O_2 are both unstable by about

Table 8. Heats of formation of the compounds OH_nF_{2-n} [1].

Compound	$-\Delta H^0_{f298}$ [kcal/mol]	$\Delta(-\Delta H^0_{f298})$	$\Delta^2(-\Delta H^0_{f298})$
H_2O	57.9		
HOF	23.5±2	−34.4±2	
F_2O	5.9±1	−29.4±2.2	5±3

Table 9. Heats of formation of the compounds $OH_n(OH)_{2-n}$.

Compound	$-\Delta H^0_{f298}$ [kcal/mol]	$\Delta(-\Delta H^0_{f298})$	$\Delta^2(-\Delta H^0_{f298})$
H_2O	57.9		
HO(OH)	32.6	−25.3	
$O(OH)_2$	15.8±1.5	−16.8±1.5	8.5±1.5

5—6 kcal/mol with respect to disproportionation into their symmetrical neighbors[24]. These intermediates correspond precisely to the example illustrated in Figure 1, where the partial charges *a* and *b* are of opposite sign and where the above disproportionations should thus always be exothermic.

Another striking example of alternating polarity is afforded by the remarkable regularity in $\Delta(\Delta H^0_f)$ values observed in the pairs of compounds X—H and X—CH_3. Where the X—H bond is very polar with X negative and H positive, then the replacement of H by the negative C-atom of CH_3 should produce a less negative increment in ΔH^0_f than when X bears a positive partial charge. This is illustrated in Table 10 taken

Table 10. Effect of the polarity of X on differences in ΔH^0_f of the compounds H—X and CH_3—X (data from Ref. [17]).

X	$-\Delta H^0_{f298}$(HX) [kcal/mol]	$-\Delta H^0_{f298}(CH_3X)$ [kcal/mol]	$\Delta(\Delta H^0_{f298})$
OH	57.8	48.0	9.8
F	64.8	56.8±2	8.0±2
CH_3COO	103.8	98	5.8
NH_2	11.0	5.5	5.5
CH_3O	48.0	44.0	4.0
NO_3	32.1	28.6	3.5
Cl	22.0	19.6	2.4
Br	8.7	9.5	− 0.8
HS	4.8	5.4	− 0.6
CH_3	17.9	20.2	− 2.3
I	6.3	3.3	− 3.0
CH_3S	5.4	8.9	− 3.5
nC_3H_7	24.8	30.2	− 5.4
C_2H_3	−12.5	− 4.9	− 7.6
C_2H	−54.2	−44.3	− 9.9
CF_3	167	178	−11
CH_3CO	39.7	51.7	−12.0
HOOC	90.5	103.8	−13.3

from data in Ref. [17]. It is of particular interest to note the effect of substitution on the polarity of a polyvalent element. Thus the replacement of H by CH_3 on either O or N or S makes the elements appear much less electronegative in the sequence shown.

5. Electrostatic Model of Polar Bonds

In a simple disproportionation reaction, the uncertainty in the enthalpy of reaction has as at least double the uncertainty in the ΔH^0_f of the intermediate species. In Tables 4 through 9 these ΔH^0_r are given by the second order differences $\Delta^2(\Delta H^0_f)$ and we see that in general they have uncertainties of the order of ±2 kcal/mol or larger. Since the electrostatic model equates these second order differences to the changes in electrostatic energies we see the major current problem in assigning values to the parameters of a more sophisticated model. It is only for the fluorine and oxygen compounds that the $\Delta^2(\Delta H^0_f)$ are sufficiently large relative to the uncertainties

in ΔH_f^0 that we can hope to uniquely assign more than one parameter.

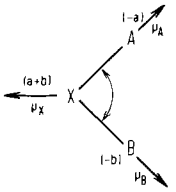


Fig. 2. Electrostatic model of the polar bond with polarization interaction and lone pair dipoles.

The most general model is illustrated in Figure 2 for the case of a divalent atom X with lone pairs attached to atoms A and B each with lone pairs. We must assign partial charges a and b to atoms in each of the bonds as before (Figure 1) and also lone pair moments μ_A, μ_B, and μ_X to each atom. We must also decide on whether or not to use a point dipole or discrete charge distribution to represent the lone pairs and how to orient them.

In the interests of reducing parameters we have chosen for the halogen atoms to represent all the lone pairs by a single point dipole centered at the nucleus and oriented along the bond axis. For oxygen, sulfur and group 6 elements, the dipole is chosen to be oriented along the line bisecting the two bonds and in the plane of these bonds. For nitrogen and group 5 elements, the dipole is stationed along the axis symmetric to the three bonds.

While the introduction of lone pair dipole moments turns out to make a physically more reasonable model[25] it does not introduce the needed nonlinearity[13]. The electrostatic energy associated with fixed partial charges and lone pairs is pair-wise additive in bonds taken two at a time and will always lead to constant second differences in ΔH_f^0 in a homologous series.

In order to obtain second order differences in $\Delta H_f^0[\Delta^2(\Delta H_f^0)]$ in a homologous series which vary we need a non-linear interaction between neighboring bonds. In the electrostatic model this can be introduced by permitting polarization of the various electron distributions. Charge-induced dipole interactions have attractive energies which are proportional to the square of the charge. If for example we consider in Figure 2 the polarization interaction between the charge $(a+b)$ on X and the atom A it can be expressed as:

$$E_{\mathrm{pol(XA)}} = \frac{-(a+b)^2}{2r_{\mathrm{XA}}^4}\alpha_{\mathrm{A}} \tag{10}$$

$$= \frac{-(a^2+b^2)\alpha_{\mathrm{A}}}{2r_{\mathrm{XA}}^4} - \frac{2ab\alpha_{\mathrm{A}}}{2r_{\mathrm{XA}}^4} \tag{11}$$

where α_A is the effective polarizability of the atom A. This polarization energy is no longer a simple superposition of the polarization produced by A and B separately as represented by the first term on the right-hand side of equation 11 but contains cross product terms (ab) which can reduce or increase the total effect depending on the relative signs of a and b. Such polarizations are also required if one is to account for the observed dipole moments of polar molecules. Fixed dipoles and fixed charges could never account for the large decreases observed in dipole moments in such sequences as CH_3Cl ($\mu = 1.87$ D) and $CHCl_3$ ($\mu = 1.01$ D)[26].

The detailed investigation of a polarization model has not been completed and so it must be emphasized that our discussion is highly speculative. Nevertheless, it is of interest to look even at the qualitative results obtained thus far. These indicate that the bonds of carbon to halogen atoms are much less "ionic" than hitherto supposed. For example in the CH_nF_{4-n} series it appears that a lone pair moment assigned to F of about 0.7 D together with a partial charge across the C—F bond of $\pm 0.7 \times 10^{-10}$ esu. will come close to reproducing the thermochemical and dipole data. Interestingly, C—O bonds have about the same properties as C—F. C—Cl bonds are characterized by a partial charge of about $\pm 0.36 \times 10^{-10}$ esu and a Cl lone pair dipole about 0.9 D. The C—Br bond has a partial charge of about $\pm 0.30 + 10^{-10}$ esu and a lone pair moment of about 0.9 D while the C—I bond has a partial charge of about $\pm 0.26 \times 10^{-10}$ esu and a lone pair moment of about 1.0 D.

For ketones and CO_2 the moments for the lone pairs on oxygen turn out to be about 0.6 D while the partial charges across the C=O bond are about double that for the C—O single bond, namely about 1.2×10^{-10} esu. It thus appears that the ionicity of double bonds is about twice that of single bonds and one might guess that the ionicity of the C≡N triple bond will be the largest of all bonds. Again, all of these results must be considered as tentative.

6. Dipole Moments

Propane and isobutane have small but measurable dipole moments of the order of 0.08 D and 0.14 D respectively. The simple fixed charge model of the C—H bond gives zero moment for both molecules even when the accurate geometries are used[18]. It was found in the original study that the small measured dipoles could be satisfactorily accounted for by polarization interactions between the charged atoms. The same situation obtained for the unsaturated olefins, aromatics and acetylene compounds where the dipole moments range from 0.36 to 0.70 D. Static moments accounted for about half or less of the observed moments and polarization the remainder[19].

When we come to polar molecules, the importance of polarization is very evident. Some time ago *Eyring et al.*[27] devised a self-consistent scheme for reproducing the dipole moments of the haloalkanes by a scheme of induced polarizations. This was extended by *Smith et al.*[28] with reasonable success. In both these schemes it is interesting to note that the value chosen for the dipole moment of the C—H bond was 0.32 D, almost precisely the value needed to fit the energies of the alkanes!

An example of the effect of polarization on dipole moment is illustrated in Figure 3 showing simple charge distributions in methyl-X and *tert*-butyl-X compounds.

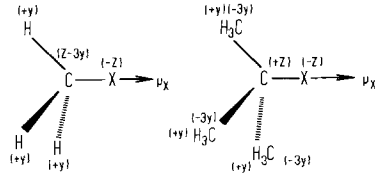


Fig. 3. Application of electrostatic model to polar methyl-X and *tert*-butyl-X compounds.

It was pointed out some time ago[29] that the difference in heats of formation of MeX and *t*-BuX varied systematically with the nature of X and ranged from values near 18 kcal/mol for hydrocarbons to extreme values of about 27 kcal/mol for strongly electronegative X. Along with this correlation we can add the observation that in addition the dipole moments of *tert*-Butyl-X are systematically larger than those of CH_3X. The polarization model is compatible with such an effect as can be seen from the charge distribution shown in Figure 3. In the t-butyl compounds all the atoms attached to the central C-atom are negative and there is relatively little electric field at this atom. In the CH_3—X compound, on the contrary, the charges of the peripheral atoms produce a strong field at the C-atom and in such a direction as to oppose the overall molecular dipole. The charges suggested here for the halogens are in accord with the conclusion that CH_3—X dipoles are smaller than those of *t*-Butyl X because of back polarization in CH_3X.

7. Conclusions

The simple electrostatic model with fixed partial charges works very well for relatively non-polar species such as hydrocarbons and silicon compounds. With these compounds the small but measurable dipole moments can only be reproduced by permitting internal polarization to take place. The polarity of the C—H bond used in this model, $\mu_{CH}=0.32$ Debye, is almost precisely the polarity required by stick dipole models. For more polar molecules internal polarization effects are no longer small and are required in order to fit the data. Research is currently underway on exploring such a model with results that can be described as encouraging. The rewards in discovering a successful model would be enormous in that they would make thermochemistry available as an accurate and practical tool for laboratory and industrial work.

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[24] It is quite possible that the instability of H_2O_2 observed in alkaline solutions proceeds first through a disproportionation into H_2O and H_2O_3 or their corresponding anions OH^- and HO_2^-.
[25] We are also exploring a physically more reasonable model in which the lone pair point dipole μ_X is displaced from the nucleus by an amount $\Delta x/2$ (in Å) with Δx determined by setting it equal to $\mu_x/4.80$. This is equivalent to setting the displaced lone pair charge equal to that of 1 electron. It turns out that this displacement avoids many problems of treating dipole-induced-dipole interactions which will depend on the 6th power of the distance and can become infinite when the polarizabilities of the atoms are large.
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Polyethylene Fibrids: Preparation and Properties[**]

By Wolfgang Gordon, Hans Joachim Leugering, and Harald Cherdron[*]

Dedicated to Professor Karl Winnacker on the occasion of his 75th birthday

Polyethylene fibrids are small fibers having lengths of up to some millimeters, which are highly oriented and which have a morphology similar to that of cellulose fibers. The preparation of polyethylene fibrids is based on shear-induced crystallization, a process in which the polyethylene crystallizes from solution under the influence of an elongated flow in the form of so-called shish-kebabs. Polymerization under shear conditions and the flash spinning of polyethylene solutions are the main processes for the preparation of PE fibrids. They may be hydrophilized by an additional process step.—Because of their cellulose-like morphology, (hydrophilized) polyethylene fibrids have interesting properties, *e.g.* high adsorption capacity and the ability to form hydrogen bonds. In addition, the possibility of undertaking chemical reactions on the surface of the fibrids should be mentioned.

1. Introduction

Attempts to supplement or replace natural polymers in paper by fully synthetic polymers constituted the starting point in dealing with one of the oldest raw materials, which has been of decisive importance in the cultural development of mankind. While the technology of papermaking has always been subject to modification and improvement, nothing was changed for centuries with respect to the raw material since its discovery by *Tsai Lun* in 105 AD. The sources of the raw material were mulberry bast, bamboo fibers and china grass in Asia, and straw and particularly rags (old linen goods) in Europe. It was as late as the middle of the 18th century before groundwood was being employed in papermaking and cellulose fibers became available from wood by different digestion processes. With the development of synthetic polymers, their usefulness for incorporation in cellulose papers was soon realized. The papers of to-day therefore contain synthetic polymers such as polyvinyl alcohol, polyacrylamide, urea formaldehyde resin and polymer lattices in quantities which vary depending on the specific application.

These polymers, however, clearly have the function of an *additive* for the improvement of certain properties and are not used as a substitute for cellulose fibers.

In the past years, efforts have been made in various places, to prepare highly oriented fibers (fibrids) from synthetic polymers, which in their morphology are similar to cellulose fibers and which therefore may also be called synthetic pulp. During the first period of this development, the main aim was to use these fibrids in conventional papermaking processes and—in contrast to the above polymers—to replace portions of groundwood or cellulose pulp. However, it was soon found that some polymer fibrids have a number of additional properties which make them valuable for quite different applications.

The preparation, properties and applications of this new form of polymer will be described using polyethylene fibrids as example.

2. Preparation of Polyethylene Fibrids

2.1. Crystallization of Polyethylene

Polymer fibrids can be obtained from solutions of crystalline polymers, because not only the crystallization kinetics but also the crystalline morphology of the macromolecular starting substance can be completely altered by varying the conditions of crystallization. Thus, for example, the crystallization of polyethylene (PE) from unstirred solutions leads to a completely different morphology than crystallization of the same polymer from solutions exposed to shearing forces.

In 1957 *Fischer, Keller* and *Till* independently observed that single crystals which develop upon cooling of static diluted solutions of polyethylene[1] have a characteristic rhomboid shape. These lamellae have a uniform thickness of about 150 Å, but their lateral dimensions can be of the magnitude of some μm. Since the polyethylene macromolecules are considerably longer than the thickness of the single crystals, it was concluded that the molecules are folded perpendicularly to the basal plane. In fact, it could be shown that on crystallization the PE macromolecules lose their statistical coil form, which they have in solution, and that they fold themselves in a meander-like fashion. The single crystals, therefore, are lamellae in which the PE macromolecules are folded in a planar zigzag conformation (see the disk-shaped parts of Fig. 5). This folded structure is, of course, not completely regular, because structural non-uniformities (molecular end groups, short chain branches) cause disorders in the crystallite constitution.

On crystallization from more concentrated solutions under non-isothermic conditions complicated superstructures (dendrites, spherulites) are formed, which, however, always consist of single crystal lamellae of the type described above. For further details see reviews by *Geil*[2] and *Wunderlich*[3].

The crystallization is completely different, however, if the PE solution is cooled with stirring[4]. Stirring by means of

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[**] Main lecture at the GDCh General Meeting, September 13, 1977 in München (Germany).

a rotating cylinder above the critical Reynold's number causes the development of Taylor whirls (see Fig. 2b), at whose edges an elongated flow is generated (see arrows in Fig. 2b). This leads to stretching of the macromolecules and thus to their orientation in the direction of the gradient of flow. The PE molecules can crystallize in this oriented state and, due to the parallel arrangement of the molecules, the change of conformation entropy $\Delta S = \Delta H/T$ is smaller than when there is no preorientation in solution.

This phenomenon is called "shear induced crystallization". Because of the smaller change of entropy, the crystallization temperature is comparatively higher than in crystallization from solutions at rest[2, 3].

It seems to be important for shear-induced crystallization, that the stretched molecular confirmation is stable over a long enough residence time, while in the case of simple shear flow (*e.g.* in the shear field next to a resting wall) the polymer coil rotates and is periodically compressed and stretched. This results in only poor orientation of the macromolecule. These differences can be seen in Figure 1, where the orientation of the macromolecules is presented as a function of the gradient of flow (slope flow rate) for elongated flow (by acceleration) and for shear flow (due to the stationary wall)[7].

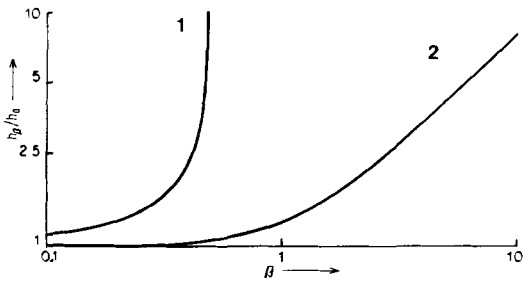


Fig. 1. Avarage elongation of the macromolecular coil h_β/h_0 for the case of elongated flow (1) and shear flow (2) as a function of the dimensionless flow gradient β (see [7]).

These modified conditions of crystallization have a decisive influence on the morphology of the resulting PE crystallites, as described in Section 3.1. The macroscopic form is modified, too. Instead of the usual powder, highly oriented small fibers are obtained upon shear crystallization. For practical use as polyethylene fibrids, they are usually cut and fibrillated (*i.e.* partially split longitudinally) by an additional mechanical treatment.

The most important processes for the preparation of PE fibrids by shear induced crystallization will be described in the following sections. Furthermore, because of their practical importance, methods for the preparation of hydrophilic fibrids will also be presented.

2.2. Shear Induced Crystallization of Polyethylene Solutions

Pennings[4] found that fibrous crystalline material is obtained upon crystallization of polyethylene solutions (about 5%) by turbulent stirring using common laboratory stirring equipment. However, the most important phenomena here can be observed better, if a "reversed" Couette assembly is used for stirring[5, 6]. It consists of one internal and one external cylinder, with the internal cylinder rotating (Fig. 2a).

If a critical Reynold's number is exceeded, the crystalline matter does not separate out uniformly on the rotating cylinder, but in periodic sections (Fig. 2a). These are places of elongated flow due to the Taylor whirls (see arrows in Fig. 2b). In a "true" Couette assembly, in which the exterior cylinder rotates, no shear induced crystallization takes place, because no Taylor whirls develop in this case.

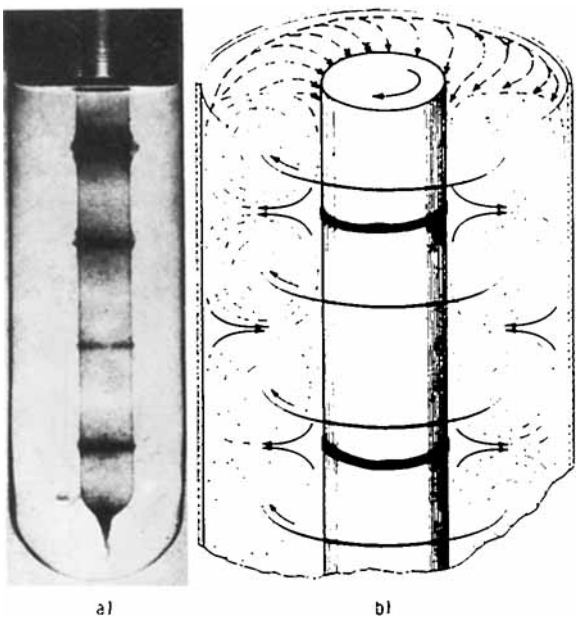


Fig. 2. a) Periodic precipitation of fibrous crystalline polyethylene on the interior rotating cylinder of a "reversed" Couette arrangement [5]. b) Schematic representation of Taylor whirls around a coaxially rotating cylinder (dotted lines). The precipitated PE crystals are marked by dark stripes [5].

A particularly important practical variant is simultaneous polymerization *and* shear induced crystallization. In this case, the suspension polymerization of ethylene with *e.g.* Ziegler catalysts is carried out under such vigorous stirring conditions that the macromolecules formed become stretched before they can crystallize in the usual zigzag conformation[8]. The polymer chains growing at the active catalytic centers require a certain time for crystallization. In the meantime, the growing macromolecules can be oriented to such an extent that fibrous polymer is obtained which has the same morphology as polymers obtained by shear induced crystallization instead of the usual polymer powder. By this process, PE fibrids can be produced with essentially arbitrary high molecular weights, which is difficult to achieve by simple shear induced crystallization of polymer solutions because of the large increase in viscosity of the solutions with increasing molecular weight of the polymer.

2.3. Flash Spinning of Polyethylene Solutions

In this process, which we may call simply the flash process[9], we are dealing with a non-isothermic crystallization of polyethylene. Firstly, polyethylene is dissolved at high temperature under pressure in a solvent with low boiling point. The superheated solution is then allowed to flow through a nozzle, which causes a high degree of orientation of the polymer molecules. Upon discharge of the solution from the nozzle, the solvent rapidly evaporates and the highly oriented polymer

instantly crystallizes in fibrous form; moreover, the sudden evaporation of the solvent causes longitudinal splitting of the fibrous material. Similarly to cellulose fibers, this material can be cut and split in refiners in order to achieve the optimum shape for various applications.

Studies by *Pickup*[10] on the hydrodynamics of the discharge of viscoelastic fluids from nozzles may contribute to an understanding of the phenomena which are of most importance in the flash process. A fluid volume element flowing along the axis is accelerated in the intake zone of the nozzle. In this zone there is elongated flow only. The geometry of the cup-like intake flow depends upon the flowrate and the viscoelastic properties of the fluid. No significant orientation takes place on entry of the volume element into the nozzle. After exit from the nozzle the flowrate of the solution increases further owing to expansion by evaporation of the solvent. The rapid evaporation also causes instant "freezing" of the elongated state of the macromolecules.

2.4. Extrusion of Multiphase Polymer Melts

Polymer fibrids with reproducible fiber length distribution can also be obtained by extrusion of polymer melts consisting of two or more phases, followed by cold elongation, pelletizing and refining[11]. Since the polymers are usually incompatible in the solid state, they split longitudinally at the phase interphase in the elongated state and polymer fibrids are obtained. Their dimensions are determined by both the degree of dispersion of the polymer melt and the degree of elongation of the extruded polymer mixture.

Addition of a hydrophilic polymer, *e.g.* polyvinyl alcohol (PVA) to the polymer melt enables concomitant hydrophilization of *e.g.* polyethylene/polypropylene fibrids. Microscopic and stereoscan photographs show that these fibrids are composed of two kinds of fibers, namely polyethylene/polypropylene fibers, with both polymers highly dispersed, and polyvinyl alcohol fibers.

2.5. Preparation of Hydrophilic Polyethylene Fibrids

Since most non-textile fibers are processed in aqueous systems, it is of great technical interest to render PE fibrids hydrophilic. Some methods used for the hydrophilization are described in the following Sections.

2.5.1. Post Adsorption

PE fibrids are capable of adsorbing a variety of water soluble organic compounds from aqueous solution. This method is technically simple, but only a part of the hydrophilization agent is taken up. Cationic, anionic and non-ionic surfactants of common structure render the hydrophilic fibers wettable, but they are only partially adsorbed and can be readily desorbed. Water soluble polymers like polyvinyl alcohol, polyethyleneimine or polyvinylpyrrolidone[12,13] effect an improved dispersibility of PE fibrids in water. In the case of PVA, the amount adsorbed can be increased by addition of salts (*e.g.* K_2SO_4)[14] or by prior reaction of the PVA with aliphatic aldehydes[15]. The same can be achieved by treatment of PE fibrids in swollen form with aqueous PVA solution[16]. The adsorption of special melamine-formaldehyde resins[17], polyoxalkylated urethane compounds[18] and acetals or ketals[19] as well as special nitrogen compounds[20–22] prevent the aqueous fiber suspension from foaming.

2.5.2. *In Situ* Hydrophilization

In the flash process, the hydrophilization agent is often added to the PE solution beforehand. While low molecular weight surfactants[23] are probably bound only after fibrid formation, in the case of high molecular compounds like polyvinyl alcohol, polyacrylamide, carboxymethylcellulose, sodium polyacrylate or polyvinylpyrrolidone one can expect a more solid anchoring by "freezing" of partially entangled macromolecules[24,25]. Thus, a higher portion of the hydrophilization agent can be bound this way.

2.5.3. Modification of Polyethylene

Special hydrophilization agents can be dispensed with if part of the polymer base is chemically modified. In this connection, copolymers of ethylene with maleic anhydride, sodium maleate, acrylic acid, sodium acrylate or allyl alcohol[26], or special block copolymers of ethylene and vinyl acetate, or also polyethylene, onto which acrylic acid is grafted, have been used[27]. The grafting step can also follow a partial oxidation step, *e.g.* with ozone[28].

3. Properties of Polyethylene Fibrids

3.1. Morphology

After comminution, PE fibrids—in contrast to cut staple fibers—have a highly branched structure of varying length and irregular diameter (Fig. 3).

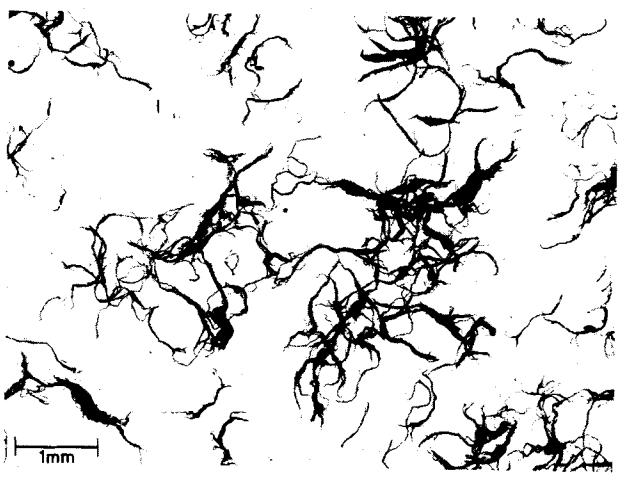


Fig. 3. PE fibrids dispersed in water.

The mean fiber length (CFL = classified fiber length)[29] of commercial PE fibrids ranges from 0.5 to 2.5 mm. Because of the low packing density, the branched fibrids take up a relatively large volume in the suspended form, thus leading to thixotropic flow peroperties of fibrid suspensions and to a high degree of hooking of the fibrids on filtration. The thixotropic flow properties are exploited by the building industry, *viz.* when Hostapulp® is added to trowelling compounds and surfacing textures. Because of this cellulose-like hooking,

papers having thermoplastic character can be manufactured on common paper machines. Since very long fibers in fiber slurries tend to cause flocculation and spinning, efforts are being directed at achieving narrow fiber-length distributions with presence of only small amounts of long fibers.

The crystal morphology of these fibrids is particularly interesting: Under the electron microscope the fibrids look like spindles, onto which disk-like structures are connected laterally, a composite structure reminiscent of a "Schaschlik" skewer (Fig. 4). For this structure, *Lindenmeyer* proposed the name "Shish-Kebab", which has been widely accepted. Figure 5 shows, how the molecular chains are arranged in this "Shish-Kebab" structure[30].

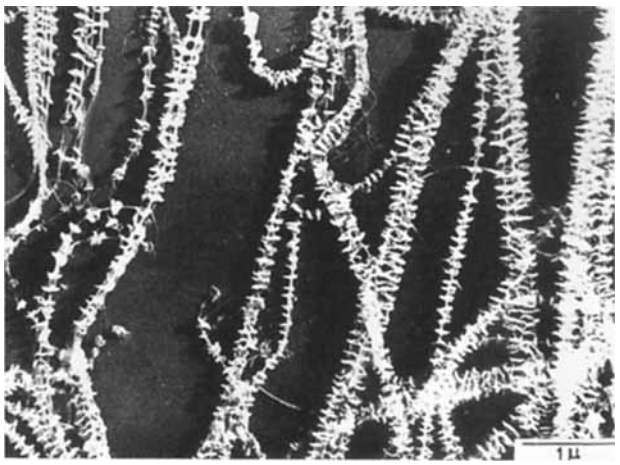


Fig. 4. Electronmicrophotographs of PE crystals obtained by shear induced crystallization [31].

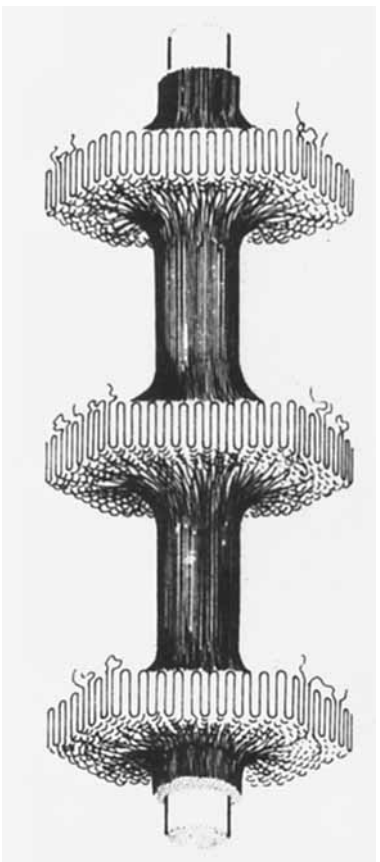


Fig. 5. Schematic arrangement of PE molecules in a Shish-Kebab structure [31].

Modern conceptions of the structure of fibrids have recently been reviewed by *Peterlin*[7]. The macromolecules of the fibril center are staggered and in the stretched state are arranged essentially parallel, while the lateral structures are formed by epitactical growth of folded molecular chains. Thus, the structures of the fibril center and of the lateral disks differ significantly. The latter can be dissolved from the fibril center by treatment with solvents or fuming nitric acid.

3.2. Mechanical Properties

Depending on the process and on the molecular weight, PE fibrids having quite different degrees of orientation and (consequently) quite different mechanical properties can be obtained.

The mechanical properties of shear induced crystals formed under isothermal conditions (see Section 2.2) are shown in Figure 6. These results were obtained by measurement of the stress/strain diagram of a fiber matte, formed around the interior cylinder of a reverse Couette arrangement, and from which the test specimen was taken perpendicularly to the cylinder axis[31].

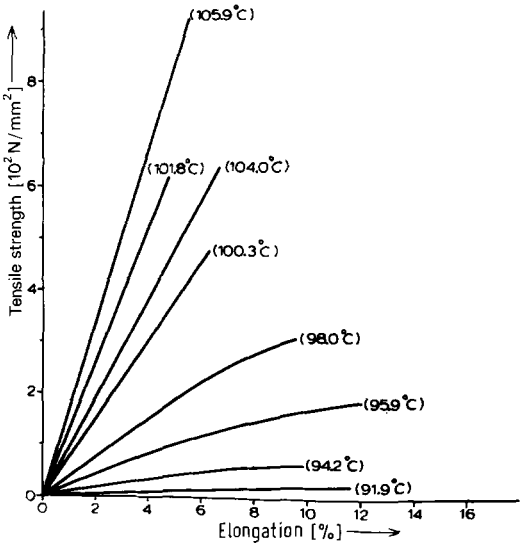


Fig. 6. Mechanical properties of PE crystal mattes obtained by shear induced crystallization [32]. Rate of stretch 3 cm/min. For details see text.

While the material obtained at 92 °C has a tensile strength comparable to that found for unoriented samples, fibers crystallized at higher temperatures have tensile strengths of up to 1000 N/mm^2. The Young's modulus of elasticity is found to increase symbatically with the increase in tensile strength. Determination of the mechanical properties of fibrids prepared by flash spinning of PE solutions, however, pose more problems, since these fibrids may contain internal cavities and the effective cross-section is not known. Even elaborate investigations provide only approximate values of the lower limit of the tensile strength (40—60 N/mm^2).

For most applications, fibrids with low single fiber strength may be used in combination with cellulose fibers, for, owing to their flexibility, they yield a paper having good strength properties. Since the mutual bonding of PE fibrids and cellulose fibers in paper is weaker than the inter-fiber bonding of cellulose fibers, the single fiber strength of the PE fibrids cannot

be exploited anyway. A content of PE fibrids is advantageous, *e.g.* for the dimensional stability (= reduced water absorption, swellability).

3.3. Thermal Properties

Since PE fibrids have two different crystalline morphologies, the DSC (differential scanning calorimeter) diagram of highly oriented fibrids shows two peaks. The peak at lower temperatures is assigned to the lamella form and the peak at higher temperatures to the stretched crystalline form of polyethylene. If the portion which crystallizes in the form of folded lamella is removed by extraction, the peak for the portion melting at lower temperatures is found to decrease[6, 31].

On melting, the stretched crystallized molecules tend to adopt the usual coil conformation, *i.e.* the molecules shrink longitudinally on melting[6]. Due to the necessary transfer of heat the process of shrinkage in a radial direction is delayed and therefore not complete. If the macromolecules melt in the exterior zone only, the are prevented from shrinking by the fibril center, which is still solid. Despite this impairment the degree of shrinkage is measurable and can be correlated with the orientation. According to *Pennings*, the shrinkage is larger, the higher the temperature of the shear induced crystallization[6].

In practice, thermal formability under pressure plays a very important role. For example, addition of PE fibrids renderes papers heat-sealable and embossible, and cardboards and corrugated papers are made considerably stiffer.

3.4. Surface Properties

The specific surface area of commercially available PE fibrids (5—10 m^2/g), measured according to the BET method, is larger than that of synthetic fibers (0.2—0.5 m^2/g) obtained by melt spinning. In some cases, surface areas of up to 100 m^2/g have been reported[32]. It is important that either a more lyophilic or a more hydrophilic character can be imposed on the PE fibrids depending on the chemical modification of the surface. PE fibrids with a large surface area have a high specific adsorption.

3.4.1. Lyophilic Properties

Because of their chemical structure and their shape, PE fibrids are good adsorbents for hydrocarbons. They adsorb hydrocarbons from water and from gases as well as from concentrated phases.

Figure 7 demonstrates the decrease in small quantities of white spirit dispersed in water on addition of PE fibrids[33]. Most of the droplets of hydrocarbons are mopped up due to the special shape and large hydrophobic surface area of the fibers.

Oil, for instance, can be thickened until a solid consistency is reached. Under specified conditions[34], PE fibrids are able to bind up to ten times their own weight of oil. The amount of oil that can be bound increases with increasing degree of fibrillation (degree of branching, see Fig. 3) and with decreasing hydrophilicity. The fibrids can, for example, be spread over oil-spills in inland waters by spraying an aqueous suspension with a fire hose. The resulting fibrid/oil mixture is, in

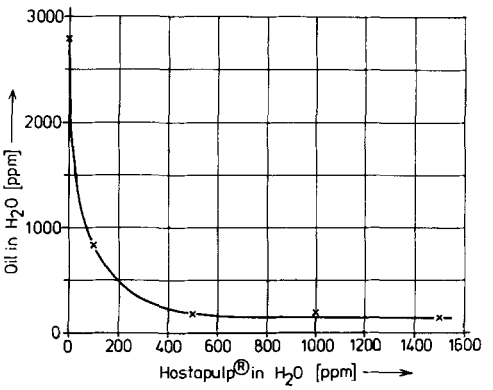


Fig. 7. The concentration of white spirit (b. p. 140—170°C) dispersed in water as a function of the concentration of added PE fibrids (Hostapulp®).

contrast to many other materials, *completely* floatable and can be removed mechanically from the water surface. Thus, PE fibrids are an invaluable material for the protection of the environment.

The removal of finely dispersed tar or nicotine droplets from cigarette smoke constitutes an important example of their use for the sorption of undesirable products from the gas phase. The specific binding capacity of PE fibrids has been found to be significantly higher than that of normal cellulose acetate filters.

3.4.2. Hydrophilic Properties

Hydrophilization not only makes the fibrids wettable, but also dispersible and thus mixable with other hydrophilic agents. The dispersibility is usually characterized by measurement of the flotation (tendency of the PE fibrids to float on account of their lower specific gravity) in 0.5% fiber suspensions (flotation factor[35]) and by measurement of their resistance to filtration (drainage factor) as defined and specified by the TAPPI Standard[36]. The dispersibility depends not only upon the nature and the quantity of the hydrophilization agent, but also largely upon the degree of slenderness and fibrillation of the fibrids. Commercial PE fibrids (*e.g.* Hostapulp®) having a high dispersibility usually contain up to 4% polyvinyl alcohol. The PVA content can be determined IR spectroscopically (peak at 3.0 μm) on molded films (of 0.1 mm thickness)[37].

In papermaking, the hydrophilization of PE fibrids is a very important factor regarding the quality of the paper. Even a small number of fiber flocs, formed from insufficiently hydrophylized fibrids, interfere in this case. Other applications, in which hydrophilization is essential, include, for instance, the production of porous pipes by wet molding and the mixing of fibrids in building materials.

3.5. Chemical Properties

PE fibrids modified with polyvinyl alcohol enable further modifications by chemical reactions on the surface. A few examples are described in the following chapters.

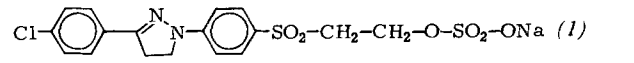
3.5.1. Formation of Hydrogen Bonds

It is assumed that hydrogen bonds, which are important for dispersibility in water, are formed not only between PE

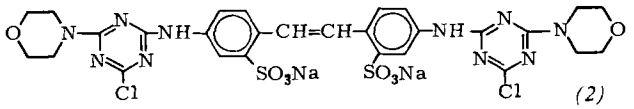
fibrids and water molecules, but also between the fibrids themselves and between fibrids and cellulose. This can be concluded from the mechanical properties of papers containing PE fibrids. Hydrogen bonding, however, is less important than in the case of cellulose fibers, since the latter, after comminution and swelling in water and shrinkage during drying, have a larger contact area than the non-swellable PE fibrids.

3.5.2. Reactions on the Surface

Polyvinyl alcohol can be fixed almost irreversibly to PE fibrids (*e.g.* Hostapulp®). This provides the opportunity for topochemical reactions, in which the reaction product is also fixed to the PE fibrid surface. This can be readily illustrated by the reactions with the fluorogenic dyes *(1)* and *(2)*; in the case of *(1)* the intermediate vinyl sulfone is the reacting agent, and in the case of *(2)* the Cl atom is substituted[38].

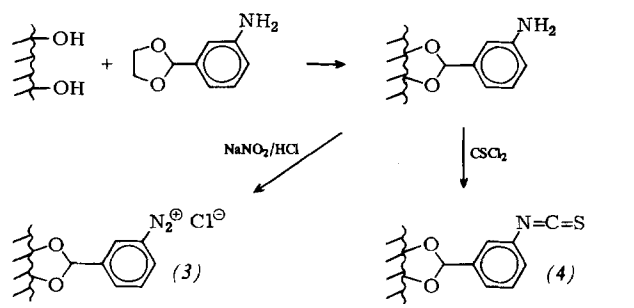


(1)



(2)

After acetalization with 2-(3-aminophenyl)dioxolane the diazonium chloride *(3)* or the isothiocyanate *(4)* can be prepared and then enzymes like trypsin or papain can be coupled to the PVA modified PE fibrids[39].



(3) *(4)*

Besides their use as carriers for enzymes, PVA modified fibrids may also be suitable as polymer catalysts and as carriers for affinity chromatography.

Further interesting examples of their practical utility include their reaction with melamine-formaldehyde (for the manufacture of decorative furnishings) and their reaction with isocyanates (incorporation into polyurethane foams). In the latter case, the PVA modified PE fibrids have the advantage of being readily dispersible in polyols. In contrast to common synthetic fibers they contribute by way of surface reaction of the OH groups to the formation of the polyurethane network. In the manufacture of polyurethane foam, PVA modified PE fibrids function not only as crosslinking agents, but also as polymeric fillers. This leads to characteristic changes in the compression curves and to improved comfort in the manufacture of seats *etc.*; this cannot be achieved when fibers are incorporated which do not have reactive groups on their surface[40].

4. Outlook

Since the oil crisis, the development of polyethylene fibrids has been governed by the raw material situation. While initial studies on these new materials were mainly directed at the replacement of cellulose fibers, the fields of application have now broadened in scope. Papermaking is still one area of usage, but only if the *special properties* of polyethylene fibrids like flexibility, dimensional stability or meltability need to be exploited. New possible applications derive from the high adsorption power or from the chemical reactivity of hydrophylized fibrids (*e.g.* analytical and preparative chromatography and biological/clinical analysis). Studies on fibrids containing fillers are still incomplete. The incorporation of (mineral) fillers opens up possibilities for the modification of mechanical and optical properties and for the enlargement of internal surface area by subsequent dissolution of the filler particles.

The objective of future studies will be the extension of these findings to fibrids of other polymers and the exploitation of the novel *combination of properties* of this new class of polymers.

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Lise Meitner: Her Life and Times— On the Centenary of the Great Scientist's Birth

By Fritz Krafft[*]

Cooperation between the three scientists *Lise Meitner*, *Otto Hahn*, and *Fritz Strassmann* in the study of the "transuranics" (1934—1938) prepared the way for the chemical identification of a first fission product of uranium by *Otto Hahn* and *Fritz Strassmann* at the end of 1938. Together with her nephew *Otto Robert Frisch*, she also gave the first theoretical interpretation of that experimental finding (barium instead of the expected radium) and suggested the inert gas krypton to be the second fission product, which *Hahn* and *Strassmann* subsequently identified (besides xenon) among the products. But she was kept from direct participation in the experiments conducted at the Kaiser Wilhelm Institute for Chemistry at Berlin—and therefore from the unrestricted claim to being co-discoverer of uranium fission—because she was an Austrian "Jewess". Thus after the "annexation" of Austria by the German Reich, the Nazi racial laws also applied to her and precluded her continuing to work in Germany. She therefore emigrated illegally *via* Holland to Sweden in the middle of 1938. There she continued to work on problems of nuclear physics under less favorable conditions until 1960. Work on radioactivity already started at Vienna had also brought her together with *Hahn* at Berlin in 1907, and she continued the work at the Kaiser Wilhelm Institute studying α-, β-, and γ-radiation and related nuclear processes. Not only because of her descent, but also because of her status of a woman in science, her fate was molded by the circumstances prevailing in Germany prior to World War II. On November 7, 1978 *Lise Meitner* would have celebrated her hundredth birthday, reason enough for recalling her lot as a woman scientist in Germany against the background of her times, which should stand as a warning to us. To that end contemporary documents could be quoted which till now were largely unknown.

"Vintage 1879"

Max Planck once jokingly said of those born in 1879 that they had been especially predestined for physics and chemistry; *Albert Einstein*, *Max von Laue*, and *Otto Hahn* were born in that year, and *Lise Meitner* should also be ranked among them, but as an impetuous female she had already been born in November 1878; she could not wait for the next year[1]. The same fact is documented in a Festschrift "Lise Meitner, Otto Hahn, Max von Laue zum 80. Geburtstag" (Beiträge zur Physik und Chemie des 20. Jahrhunderts)[2]; the contributions are arranged according to their ages: *Meitner* (born November 7, 1878), *Hahn* (born March 8, 1879), *von Laue* (born October 9, 1879). Therefore the name of *Lise Meitner* will also be found alongside those of *Einstein*, *Hahn*, and *von Laue* at the celebrations planned for next year to commemorate the centenary of those German Nobel Laureates in physics and chemistry.

Lise Meitner is to be regarded as one of the most important women in science, whose name ranks on a level with those of *Marie Curie* and her daughter *Irène Joliot-Curie*. *Albert Einstein* therefore once named her "the German Madame Curie". It was not only her quiet female charm, her elegance, her kindness, and cordiality, but also her quality as a physicist of equal standing that gained her admittance to the circle of contemporary physicists. In addition, her femininity also endowed the Berlin circle of scientists of the twenties and early thirties[3] with an exceptional quality that will also become the jubilee triumvirate in 1979. Being "older" than the others, however, she will have her own, earlier celebration, although she always tried to avoid such celebrations of her person and her achievements. Let us therefore consider not her famous historical achievements in the fields of nuclear physics (and chemistry)—that has already happened more often than she would have liked, for example in this journal[4], both during her lifetime[5] and in obituary notices[6] about her long, full, but also hard life—but instead her lot as molded by the times in which she lived[7].

Of the four scientists she certainly led the hardest life—being a woman on the one hand and of Jewish descent on the other. However, that did not make her in the least bitter, but reinforced her natural sense of fairness and formed and kept awake her political thinking. She never worked on the principle that other people should think and act like herself, and even continued to feel friendship for other people after they had disappointed her in precisely that point, as she clearly told them. That characteristic also distinguished her as a teacher and a member of a team; *Fritz Strassmann* referred to the years spent together at Berlin at the Kaiser Wilhelm Institute for Chemistry when he wrote[8]:

> "... it turned out that she deserved just as much respect in her taking care of, and in the training and guidance of the rising scientific generation as in her character as a human and scientist. Herself being inspired by an indefatigable interest in work, she ... knew that in the long run it better serves the ends of research and researchers not to force one's own working speed upon the co-worker; and what

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is more remarkable, she had the self-control to act on that judgment."

From Vienna to Berlin

Lise Meitner was born at Vienna on November 7, 1878 as the third of eight children of a lawyer. Both her parents had Jewish ancestors and her father was a Freethinker, but all the children were baptized and *Lise* was brought up as a Protestant. Even as a child she showed a great interest in mathematics and the working of nature and its causes[9], but in the late 19th century it was still too unusual for a young girl to become a student, especially a science student. So she followed her parents' will and after she left school—not yet with the "Matura" (school leaving certificate) which permits study at a university—she first qualified as a teacher of French, before she was coached privately along with two other girls for the "externe Matura" (external school leaving examination) at the Academic Gymnasium at Vienna, a boy's school. *Arthur Szarvasy* taught her and two other young ladies mathematics and physics. At that time he was a lecturer at Vienna University and later became professor of experimental physics at the Technische Hochschule in Brno. Right until the end of her life she remembered him as a extremely gifted teacher who could not only present the subject matter of mathematics and physics in a most stimulating way but could also—owing to his position at the University—show his girl students new physical apparatus, which would have been impossible at a school. Together with three other girls out of fourteen, *Lise Meitner* passed her Matura examination in 1901 and she began to study physics, mathematics and philosophy—the latter still being a compulsory subject. At the same time she also completed her probationary year at a girls' school in order to keep open the possibility of supporting herself as a teacher if the need should arise. At University she was especially impressed by *Ludwig Boltzmann*'s lectures (1902—1906), which she remembers to have been delivered with enthusiastic passion, but which did not mention the new developments which had been contributed to theoretical physics by *Max Planck* and *Albert Einstein*. *Anton Lampa* too, who directed the practical laboratory courses (which had been equipped with extremely primitive apparatus)[10], was rather sceptical towards modern physics. He had been influenced by *Ernst Mach* and was more interested in epistemological and philosophical questions than in real physics—in the opinion of *Lise Meitner*. Her doctoral thesis "Heat Conduction in Inhomogeneous Materials" was written under the supervision of *Franz Seraphin Exner* and his assistant *Hans Benndorf*. Female candidates for a doctor's degree were still something out of the ordinary at that time at Vienna, too. The first woman postgraduate had been *Gabriele Baronin Possander* (medicine, 1897); *Adele Gräfin Wartensleben* (classics)—who later founded the first commercial school for girls at Vienna—had been a pioneer at the faculty of philosophy; and *Olga Steindler* was the first woman to gain a doctorate in physics in 1903. *Lise Meitner* and *Selma Freud* followed in 1906.

In her thesis *Lise Meitner* had proved experimentally that Maxwell's formula for conduction of electricity in inhomogeneous materials also holds for thermal conduction in mercury ointments. Her second paper dealt with "Conclusions that are to be drawn from Fresnel's reflection formulae"; it was published in 1906 in the proceedings of the Preussische Akademie der Wissenschaften. For her later work it was decisive that after *Ludwig Boltzmann*'s death his institute was taken over temporarily by *Stefan Meyer* and that she could go on with her experimental work. *Meyer* had devoted his attention to the new field of radioactivity. Together with *Egon von Schweidler* he had discovered the magnetic deflection of "radium rays" (later called β-rays) in 1910, and he worked intensively on methods of measurement of radioactive matter. Using ThB and AcB preparations, *Lise Meitner* carried out measurements on the absorption of α- and β-radiation with Pt, Au, Ag, Cu, Sn, and Al[11]. This was her introduction to modern physics. At that time she heard *Max Planck*'s name for the first time, because after *Boltzmann*'s death he had been invited to take his post at Vienna and came to Vienna to look around the institute. That raised her desire to spend several semesters at Berlin in order to gain "a real understanding of physics". Her parents complied with her desire and granted her a small allowance[12]:

> "When I registered with *Planck* at the University in Berlin, so as to attend his lectures, he received me very kindly and soon afterwards invited me to his home. The first time I visited him there, he said to me: "But you are a Doctor already! What more do you want?" When I replied that I would like to gain some real understanding of physics, he just said a few friendly words and I did not pursue the matter any further. Naturally I concluded that he could have no very high opinion of women students, and possibly that was true enough at the time."

Admittedly at that time *Max Planck* was no longer absolutely hostile towards women students, but he did not advocate them without reservation either. That would have contradicted his rather conservative attitude. But *Lise Meitner* could not have known that.

In 1896 girls had been granted permission to take the school leaving examination (Abitur) in Germany, and the general admission to the universities was just a question of time—it was granted by law in 1900, in Prussia in 1908. The contemporary discussion on the *pro* and *contra* is documented by a collection of comments of 104 university professors and lecturers, when they answered the following questions of *Arthur Kirchhoff*: "What are the reasons to be stated in general, and from the special point of view of your discipline, for or against women students at universities? What are the preliminary studies the young girls should receive, and is it permissable for both sexes to study together at university?"[13]. *Max Planck* was one of the "experts" and among other things he wrote[14]:

> "In theoretical physics, the subject which I represent, that question has not as yet become so acute that it would require a special statement as far as I am concerned ... If a woman has a special gift for the tasks of theoretical physics—which does not happen often, but it does happen sometimes—and moreover in herself she feels moved to develop her gift, I do not think it right—both personally and impersonally—to refuse her the chance and means of studying for reasons of principle; *if it is at all compatible*

with academic order, I shall readily consent to their admission—*on approval and always revocably*—to my lectures and my practical courses, and in that respect up to this point I have had nothing but favorable experience.

On the other hand I must keep to the fact that such a case must always be regarded just as an *exception* ... Generally it cannot be emphasized enough that nature herself prescribed to the woman her function as mother and housewife, and that laws of nature cannot be ignored under any circumstances without grave damage, which in the case under discussion would especially manifest itself in the following generation."

Of course, *Lise Meitner* was not aware of that conservative point of view, which was even sanctioned *de jure* in 1907 at Berlin (unlike Vienna). Nor did she ever experience its effects, because *Planck* seems to have realized very soon that the young lady from Vienna was one of his approved gifted exceptions with the "inner urge" for physics. Not only was she one of the older students and assistants whom he invited to his home, but a warm friendship also developed between the *Plancks*, their daughters, and *Lise Meitner*[15]. In 1912 she became his assistant and she held that post until mid-1915, when she volunteered as a X-ray nurse in a hospital on the Austrian front, after she had attended special courses at Berlin-Lichterfelde hospital.

Besides attending theoretical lectures, *Lise Meitner* wanted to continue experimental work, as she had already done at Vienna. So she applied to the head of the institute of experimental physics at Berlin—*Heinrich Rubens*—and asked for a place in his laboratories. The only place *Rubens* was able to offer her was one in his own private laboratory, where she could work "under his direction, that is, to a certain extent with him"[16]: "Now it was quite clear to me [*i.e. Lise Meitner*] then, as a beginner, how important it would be for me to be able to ask about anything I did not understand, and it was no less clear to me that I should not have the courage to ask Professor *Rubens*." When—owing to those considerations—she hesitated to answer, *Rubens* added that *Otto Hahn* had indicated that he would be interested in collaborating with her. *Hahn* wanted the help of a physicist for his new field of radiochemistry which he had introduced at Berlin and in which he had qualified for inauguration as an academic lecturer (Habilitation) in 1907. *Lise Meitner* had already worked on radioactivity as a physicist. Having spent almost a year in America, *Hahn* was accustomed to collaboration with young women who were of the same age. He even had a marked soft spot for the "weaker" sex which he preserved to the last. "... and *Hahn* himself came a few minutes later. *Hahn* was of the same age as myself and very informal in manner, and I had the feeling that I would have no hesitation in asking him all I needed to know. Moreover, he had a very good reputation in radioactivity, so I was convinced that he could teach me a great deal."

But there was a difficulty. *Otto Hahn* did not work at *Rubens*' institute, but instead at the institute of the chemist *Emil Fischer*. And everybody knew that *Emil Fischer* cherished a strong aversion to women in the laboratories. Later on he told *Lise Meitner* that this dislike "stemmed from his constant worry with a Russian student lest her rather exotic hairstyle result in its catching fire on the Bunsen burner". So he refused *Lise Meitner*'s request to work together with the male students in the laboratory of the chemical institute directed by *Otto Hahn*. But there was a chance: In the summer of 1906 *Otto Hahn* had come to *Emil Fischer* with good recommendations from *Ernest Rutherford* and *Sir William Ramsay* and for his radiochemical work *Fischer* had placed at his disposal a room in the basement of the institute that had once been used as a carpenter's workshop (Holzwerkstatt), and that room had a detached entrance[17]. There she was allowed to work, provided she did not enter those rooms of the institute which were used by male students. *Lise Meitner* reported that later, when the attendance of women at university had been officially sanctioned even in the Prussian city of Berlin (1908/09), he immediately lifted that restriction.

What initially appeared to be the usual kind of discrimination—although *Lise Meitner* did not feel that way, since she was only interested in experimental work—soon turned out to be a great opportunity. Even so, it still happened that when the assistants of the chemical institute met her and *Hahn* they somewhat obviously greeted them with: "Guten Tag, Herr Hahn!"[18]. However she was soon admitted to the circle of the Berlin scientists through *Max Planck*, *Emil Fischer*, *Heinrich Rubens*, and *Otto Hahn*. She met *Max von Laue* at *Planck*'s lectures and at his house and other young physicists like *Rubens*' assistants *Otto von Baeyer*, *James Franck*, *Gustav Hertz*, *Robert Pohl*, *Peter Pringsheim*, and *Emil Regener* particularly at the Physical Colloquy. Not only in the twenties, but as early as 1907 that colloquy had been an intellectual center of excellence, where the leading authorities from all over the world gave lectures on the most recent results in physics, chemistry, and astrophysics. "It was quite extraordinary what one could acquire there in the way of knowledge and learning"[19]. At first, *Emil Fischer* had been very sceptical towards the "new-fangled" discipline of radiochemistry and he had accepted *Otto Hahn* merely because of his teachers' recommendations, but as soon as the first successful results were announced from the "Holzwerkstatt" he changed his mind and stood by the young people, who had formerly been left to their own resources, encouraging them where possible—and later on he obtained excellent possibilities of advancement.

The basis for these developments was the close and complementary collaboration of *Otto Hahn* and *Lise Meitner*. What originally had been meant to be a short stay at Berlin in order to benefit from further education turned into more than thirty years of a very cordial friendship and a successful scientific collaboration, which was only terminated in mid-1938 by the Nazi race laws.

As long as she stayed in German, she never had a German passport—even after March 13, 1938, the day of the "annexation" of Austria by the German Reich—but she had worked as a physicist in Germany and there she had gained her reputation: Since 1908 the *Hahn-Meitner* partnership had become a byword among experts, like the *Hahn-Meitner-Strassmann* team in the mid-thirties. When her old friend from Berlin, *Elisabeth Schiemann*, a specialist in plant genetics, asked her in 1947, when they met in London, whether she would not consider going back to Austria, she answered—as she wrote in a letter from June 8, 1947, to *Otto Hahn*[20]—: "I couldn't go *back* to Austria, since I never held a post there, but in Germany." It must have been grievous

for her to draw the possible conclusion from the answer that Austria could set up a post for her that "they do not want me in Germany?" Her real sphere of activity had been Germany and her pathway had been directed by the situation prevailing at various times in Germany. In Sweden she always felt an exile—mainly because she never gained a perfect command of the language—although facilities for work (albeit modest facilities) had been placed at her disposal there. Once having revisited Germany with rather mixed feelings on the occasion of the commemoration held in honor of Max Planck in April 1948 she always enjoyed subsequent visits to Germany. After the war she used all her influence abroad to further the international reinstatement of German scientists. She also helped a great number of colleagues—whether they were friends or not—to get over the first hard post-war years by sending them food parcels. But she could not make up her mind to "come back" to Germany—although *Fritz Strassmann* and *Otto Hahn* had offered her the post of her successor, *Josef Mattauch*, in 1947, *i.e.* then the post of the head of the old Kaiser Wilhelm Institute for Chemistry (now called the Max Planck Institute) which had been transferred to Mainz. Some years later she might have accepted that offer to return to her old sphere of activity, but on December 21, 1947, she wrote to *Strassmann*[21]:

> "The question you asked me in your last letter is rather fateful, and I have tried to think it over with all its consequences. Accordingly, it seems to me that I should be better informed before I can reach a decision with a clear conscience; above all I ought to know who are the present members of the staff of the chemical and physical departments. Quite frankly, if the inquiry hadn't been from you, my answer couldn't have been other than "No", although the longing for my old sphere of activity has never ceased. But what is left of that circle and what does it look like in the minds of the younger generation? Add to this the fact that I'm neither gifted nor inclined to ignore things that are depressing. I closely followed all the horrible events Hitler's system had brought along with it, and tried to understand them on the basis of their reasons and consequences; and that means that my view of various problems will probably differ from those of the majority of my German friends and colleagues. Would we be able to understand each other? And certainly mutual human understanding is the essential basis of a real collaboration. I have no doubts about you, but that is not enough, you know".

And on June 6, 1948, she wrote to *Hahn*[22]:

> "... In any case I believe that I cannot accept the post at Mainz. I am not afraid of unfavorable living conditions, but I do have considerable scruples about the intellectual mentality. If my view about anything which doesn't belong to physics were to differ from that of my colleagues, it would certainly be met by the words: Of course she doesn't understand the German situation, because she is an Austrian, or, because she is of Jewish descent. I also stressed those scruples when I wrote to *Strassmann*, and he didn't reply except by repeating his assertion of how important I'd be to the institute. So he didn't dare refute my scruples. That means that I couldn't count upon the confidence of the younger colleagues which I formerly had and which, in my opinion, is always—and particularly nowadays—the most important basis of good collaboration... It would become a fight similar to that which I had fought from '33 to '38 with very little success—and today it is very clear to me that it was a grave moral fault not to leave Germany in '33, since in effect by staying there I supported Hitlerism. While those moral scruples don't exist today, in view of the general mentality, my personal situation wouldn't differ much from my situation at that time, and I wouldn't really have the confidence of my colleagues, and therefore I couldn't really be of any use ..."

So only the memory of the years shared at Berlin were left to her—in the meantime *Otto Hahn* himself had become president of what was now called the Max-Planck-Gesellschaft and lived at Göttingen.

At the Kaiser Wilhelm Institute for Chemistry at Berlin-Dahlem

After a few years *Emil Fischer* assigned *Otto Hahn* and *Lise Meitner* a further room in addition to the former "Holzwerkstatt", where they could carry out their radiation measurements. From the very first *Alfred Stock*, head of the inorganic department, had placed a room in his private laboratory at *Hahn*'s disposal, where he could carry out his chemical studies and which he had been able to keep when *Alfred Stock* was succeeded by *Franz Fischer*. So the small "radioactive" team had three rooms at their disposal[23], after *Lise Meitner* had been given access to the other rooms. Now she could also participate in purely chemical work, like the fractional crystallization of radioactive preparations. Their first joint studies concerned the absorption of β-radiation of the radioelements. Although the experimental "verification" of a theory due to *Heinrich Willy Schmidt*—that the absorption of homogeneous β-radiation should follow an exponential law—which they provided by exposing aluminum to various kinds of β-radiation[24], later on turned out to be wrong, the studies and their results afforded the ways and means for the discovery of new β-emitters and for the first analysis of radioactive preparations by way of magnetic β-radiation spectra (together with *Otto von Baeyer*). Moreover, those investigations were also the starting point for *Lise Meitner*'s later work on β- and γ-radiation, in which her staff then became engaged. The application of radioaktive recoil to the discovery and separation of new disintegration products from active precipitates (1909) discovered by *Otto Hahn* was also instigated by *Lise Meitner*[25].

Shortly afterwards completely new working facilities became available[26]: In 1887 the Physikalisch-Technische Reichsanstalt had been founded at the instigation of those industries which had a physical and technical slant, and the demand soon arose for a corresponding chemical institute. The plan took shape in 1905 and in 1908 the "Verein Chemische Reichsanstalt" was founded with leading chemists from German universities and from the chemical industry as members (*Emil Fischer, Walther Nernst, Carl Duisberg, et al.*). *Ernst Beckmann*, at that time director of the laboratory for applied chemistry at Leipzig, was persuaded to become the president. In spite of considerable funds raised by the member corporations, the plan could not be realized, because the Reich was unwilling to meet the high costs of maintenance.

However, facilities were made available by the "Kaiser Wilhelm Society for the Advancement of the Sciences" which was proclaimed on October 11, 1910, by Kaiser Wilhelm II at the centenary of Berlin University. The "Verein" decided to join the Kaiser Wilhelm Society in order to found a chemical institute. On December 23, 1911, the contract was signed: The "Verein Chemische Reichsanstalt"—*Emil Fischer* was then chairman of the executive committee—declared their willingness to bear the greater part of the building costs and half the running costs (staff and equipment) of that institute, which was now to further pure research in contrast to the initial intentions. The institute was built in record time and together with the Kaiser Wilhelm Institute for Physical Chemistry and Electro-Chemistry—likewise sponsored by the Leopold-Koppel-Stiftung—the Kaiser Wilhelm Institute for Chemistry at Berlin-Dahlem was the first of the Kaiser Wilhelm Institutes to be established. The inaugural ceremony took place on October 23, 1912. *Ernst Beckmann* was appointed director and head of the department for inorganic and physical chemistry; *Richard Willstätter*—head of the department for organic chemistry—and *Otto Hahn*—head of a small department for radiochemistry—also became academic members (Wissenschaftliche Mitglieder).

In 1916, *Alfred Stock* succeeded *Willstätter* as director. *Beckmann* retired at the end of 1921. The rooms of his department were then occupied by *Kurt Hess*, whose department was completely supported by the IG Farbenindustrie A.G. from 1931 when it assumed the status of "guest department". In 1924 *Otto Hahn* had been appointed "Deputy Director" in order to prevent him from accepting the offer of a chair at the Technische Hochschule of Hannover, and he became executive director when *Stock* retired at the end of 1926. Since *Stock*'s department could not be continued, *Hahn* was made head of the whole institute in 1929, which position he held until he became president of the Kaiser Wilhelm (Max Planck) Society after World War II.

Lise Meitner initially joined *Hahn*'s department at the Kaiser Wilhelm Institute as a guest, but had already been appointed "Wissenschaftliches Mitglied" by 1913.—The University of Prague had offered her a lecturer's post with prospects of a professorship.—From 1912 to 1915 she was still *Max Planck*'s assistant, then she worked in an Austrian hospital at the front until the autumn of 1917. In 1917 she became the head of a department of her own, set up through *Emil Fischer*'s good offices with I.G. Farbenindustrie A.G.[27]. She was also given the title of professor. The department for radioactivity was divided into a "chemical-radioactive" *(Hahn)* and a "physical-radioactive" *(Meitner)* department. However, it continued to be budgeted for as a single unit, the "*Hahn/Meitner* department", until *Otto Hahn* became director and the other departments were dissolved.

At the end of 1921 the "Verein Chemische Reichsanstalt" was dissolved and succeeded by the "Emil Fischer Society for the Advancement of Chemical Research", which till then had born almost the entire costs, while the Kaiser Wilhelm Society had provided only a very small extra allowance. However, it was not only the different financial basis which had created new possibilities for research since 1912. Probably even more important with regard to the subsequent chemical and physical investigation of natural and later also of artificial radioactive substances was the move to a newly erected building. The "Holzwerkstatt" had become radioactively contaminated, and it would soon have been impossible to study weakly radioactive substances. Nevertheless, *Otto Hahn* and *Lise Meitner* learnt from experience. In the new building they worked with extreme care and discipline from the very first, and so did their staff (*e.g.* smoking was prohibited in all the laboratories). As a result there was practically no radioactive contamination to be found in the laboratories until they were moved to Tailfingen in 1944, and they could still work with extremely weak emitters that could barely be detected by the counters available at that time.

Their team work—which in spite of the breaks during the First World War had already led to the discovery of the parent of actinium, *i.e.* "protactinium", in 1917[28] came to an end in 1920. *Lise Meitner*'s department for radiophysical work had then been set up and she had been given assistants of her own, thus enabling her to start independent work. It was not before the autumn of 1934 that *Lise Meitner* and *Otto Hahn* again started working as a team—while simultaneously conducting separate investigations in their respective departments with their own staff. In the meantime, *Lise Meitner* had been occupied particularly with physical research into α-, β-, and γ-radiation and related nuclear processes. Her studies on secondary β-radiation are an outstanding example: In 1925 she decided the controversial question concerning the sequence of fast nuclear processes by proving that the secondary β-radiation derives from the electron shell of the atom formed by the transformation. So γ-radiation had to succeed β-transformation[29]. She did not develop new apparatus, but she introduced *e.g.* Wilson's cloud chamber, which had hardly been used since its invention (in 1911), to Berlin and together with her staff she introduced refinements so that it could be used for the study of slow electrons. She also succeeded in taking the first pictures of traces of positrons excited by γ-radiation[30], and she was one of the first to demonstrate pair production (electron/positron) from high-energy γ-radiation.

In 1934 a new chapter began in nuclear physics. The neutron had been discovered by *James Chadwick* in 1932 and artificial radioactivity by *Irène Joliot-Curie* and *Frédéric Joliot* in 1934. *Enrico Fermi* then realized that the neutron—being devoid of electric charge—is especially equipped to penetrate heavy atomic nuclei where they would trigger nuclear reactions. This field of research led *Lise Meitner* and *Otto Hahn* to embark on a further team project—at that time when she, according to her later judgment[31], should long have left Germany like so many other intellectuals.

The Years between the Wars in Germany

"Sex" and "Race"

At the end of the nineteenth century universities had begun to open their doors to women in the German Reich[32]. During the World War I, girls and women had unselfishly given of their best in various fields. And that undoubtedly accelerated the general admission of women to teaching positions at universities[33], after the introduction of universal suffrage in 1918. In the very same year, the first woman passed her "Habilitation" examination; she was the physicist *Hedwig Kohn*

(born in 1887 at Breslau) at the University of Breslau. In the year 1919, there followed the anatomist *Adele Hartmann* (1881 Neu Ulm—1937 Munich) at Munich, the mathematician *Emmy Noether* (1882 Erlangen—1935 Bryan, Penn./USA) at Göttingen, the archaeologist *Margarete Bieber* (born 1879 Schönau, West-Prussia) at Giessen, and the Germanist *Agathe Lasch* (1879 Berlin—1934) at Hamburg. At the Prussian universities women did not have the chance and right to qualify for a professorship (Habilitation) before a corresponding decree was issued by the Prussian Minister of Science, Arts, and Education on February 21, 1920[34] in reply to a petition of the philosopher and disciple of *Edmund Husserl*, *Edith Stein* (1891 Breslau—1942 Auschwitz), lodged on December 12, 1919. In 1922 *Lise Meitner* became the second woman to receive the *venia legendi* in physics at a German university, and the first one within Prussia. Next came *Herta Sponer* (born in 1895 at Neisse) at Göttingen in 1925[35].—Keeping in mind the novelty of female university lecturers, it is interesting to note that the subject of *Lise Meitner*'s inaugural lecture ("Problems of Cosmic Physics") was reported in the press, due to a "Freudian slip", as "Problems of Cosmetic Physics"[36]. Of course, she was exempted from other obligations which normally go with Habilitation.—Before World War II there were only two women in Germany who received the *venia legendi* in chemistry: *Maria Lipp*, née *Bredt-Savelsberg* (1892 Stollberg—1966 Cologne), 1923 at Aix-la-Chapelle, and *Gertrud Kornfeld* (1891 Prague) 1928 at Berlin.

Apart from *Maria Lipp* all the women mentioned above, like most of the other women who had been university lecturers or instructors, fell victim to Paragraph 3 (the so-called "Arierparagraph": retirement of dismissal of civil servants of non-Aryan descent) or Paragraph 4 (dismissal for political reasons) of the "Gesetz zur Wiederherstellung des Berufsbeamtentums" ("Law for the Re-establishment of the Professional Civil Service")[37] and were discharged or dismissed in 1933/34—*Lise Meitner* lost her authority to teach at Berlin University ("Lehrbefugnis") on September 6, 1939—or they fell victim to the Nazi regime's fundamental aversion to female university lecturers. Of those mentioned, *Margarete Bieber*, *Hedwig Kohn*, *Gertrud Kornfeld*, *Emmy Noether*, and *Herta Sponer* had to emigrate in 1933, and in 1938 *Lise Meitner* and *Edith Stein* escaped to Holland, where the latter was arrested in 1942 and deported to Auschwitz. Thus the well-known losses to German science from 1933 to 1939 resulting from racial and political prosecution by the Nazi regime or by voluntary emigration[38] affected women to a much greater extent, and meant a great setback to the academic feminist movement in Germany. It could be overcome only little by little after World War II[39]. *Lise Meitner* actively supported these efforts, especially after the war, in Sweden, America, Germany, and Austria, and she lectured on her own area of research and on general physical topics at various meetings of women[40].

In 1933 she had not yet been affected personally. The withdrawal of her "Lehrbefugnis" because of her Jewish descent (in 1922 she had become "Privatdozent" and in 1926 appointed extraordinary professor at Berlin University) did not involve any decisive changes, for she had never given any lectures at the university and for the time being she was still allowed to attend the Physical Colloquy at Berlin. Unlike the universities and other Kaiser Wilhelm institutes the K.W.I. for Chemistry was not completely subject to legislation concerning the Civil Service, owing to the fact that it was sponsored by the Emil Fischer Society. Therefore there was no need for any particular intercession for colleagues who were affected—unlike the universities, academies, and public hospitals, where some courageous people stood up for their Jewish colleagues, although in vain[41]. Besides, *Lise Meitner* was not subject to direct public prosecution or discrimination because she was an Austrian (*i.e.* an alien).—All that necessarily changed after the "annexation" of Austria by the German Reich on March 13, 1938.

From that day on, what had begun before the eyes of the German people on April 1, 1933, the "Day of the Boycott of Jews", was intensified. It culminated preliminarily in the organized pogrom of the "Reichskristallnacht" of November 9, 1938, and the consequences that followed the "Atonement of the Jews", ordained on November 12 and completely eliminated Jews from business and cultural life[42]: The Jewish congregations, till then corporations of public law, were declared private associations (March 28); the orders against "camouflage of Jewish trade and business" (April 22), on the declaration of Jewish properties of more than 5000 RM (April 26), and on the registration and special marking of Jewish businesses (June 14) were enacted; the so-called "action against antisocial elements" went into effect (June 14); identity cards for Jews became compulsory after January 1939 (June 23); the licences of Jewish doctors were cancelled on September 30, 1938 (July 25); Jews were to bear the names Sarah or Israel after January 1, 1939, if the name was not already clearly recognizable as Jewish (August 17); the licences of Jewish lawyers were cancelled on November 30 (September 27); the passports of Jews were marked with a "J" (October 5). By November 15 all Jewish children were excluded from general attendance at school; on November 28 housing restrictions came into force; and on January 17, 1939, the protection of tenants was cancelled; while the law on the "Aryanization" of Jewish business had already been enacted on December, 13. On October 28, 1938, about 17000 Jews "having no nationality" had been expelled from Germany over the Polish border, and after the "Reichskristallnacht" more than 26000 Jewish men had been arrested on November 12—and on January 30, 1939, Hitler, in front of the Reichstag, announced "the annihilation of the Jewish race in Europe" in the case of war (to which all visible signs were already pointing). The inferno began, but it had long been coming; and anyone was considered at "Jew" who could not prove "Aryan (*i.e.* non-Jewish) blood" for several generations.

Misinterpretation of the Situation and Lack of Resistance

In the capital Berlin above all, and especially among the scientists working there, everybody should have been conscious of what had been happening since the founding of the Third Reich in 1933. The considerable anti-Semitic sentiment of the twenties was legalized. During the twenties within the scientific community *Albert Einstein* had been particularly affected, but the solidarity of the Berlin scientists under the leadership of *Max Planck* had been able to compensate for the bias of the general public; now (1933) the academy of Berlin and its "president" *Max Planck* dropped him[43]. However, that was only the prelude, opened by the demand of

the Reichskommissar in the Prussian Ministry of Education to start disciplinary action against *Albert Einstein*, who was on a lecture tour of the United States and had reported there on the first signs of arbitrary actions against Jews and persecution in Germany. *Planck*, who had invited *Einstein* to the Berlin Academy 20 years previously, did not approve of *Einstein*'s attitude, saw no possibility of arbitration—and left for several weeks' holiday in Sicily. In February, *Otto Hahn* had left to lecture for several months in America, and in a long interview published in "The Toronto Star Weekly" on April 8 he still denied American newspaper reports on the persecution of Jews; but in a letter of May 4[44] he reported to Max Planck on the American reactions on dismissals of Jews and urgently asked him to intervene. Meanwhile (on April 7, 1933) the "Gesetz zur Wiederherstellung des Berufsbeamtentums" had of course been proclaimed and many scientists and other scholars had lost their posts at the universities or had been suspended (for the time being on full pay, however). Thereupon many of them had emigrated, while others, like *Erwin Schrödinger*, although unaffected, followed them voluntarily in order to express their disapproval of such arbitrary acts, or, like *Werner Heisenberg*, had to be prepared for their dismissal because they had declared themselves to be against the removal of important Jewish colleagues[45]. *Otto Hahn*, who was then safe as director of the Kaiser Wilhelm Institute and entitled to lecture at Berlin University as a member of the Berlin academy, withdrew from the faculty of the University as soon as he returned from America in July 1933. He reports[46] that he had been informed in America by personal letters from home, how Jewish professors and colleagues were being treated. On the basis of the close contacts between *Max Planck*, *Max von Laue*, *Otto Hahn*, and *Lise Meitner* and the nature of their mutual correspondence after 1938 it may certainly be concluded that it was *Max von Laue* and especially *Lise Meitner*, who had informed him about the events in Germany and Berlin. It was also *Lise Meitner*, who in April had informed *Max Planck* (while he was in Sicily) about occurrences in the adjacent Kaiser Wilhelm Institute for Physical Chemistry and had told him that *Fritz Haber* intended to resign from the directorate, having been dismissed from his other posts. At the insistence of *Lise Meitner*, *Max Planck* returned to Berlin at the end of April in order to attend to his duties as the president of the Kaiser Wilhelm Society. (In July 1946 he reported that to *Max Born*, one of the emigrants from 1933, when they met at the Newton celebration in London[47].) No one but *Lise Meitner*—on the basis of long years of cordial friendship with her old teacher[48] and because of her courage and feeling for fairness—seems to have been capable of that "presumption" demanded by the times. She did not have a position that allowed her to take any action, and as a "Jewess" she was hardly able to satisfy her feeling of equity by action. But haste was needed, and her friends *Max Planck* and *Otto Hahn* (who held such positions) had returned too late to reverse what had happened:

Planck made up his mind and tried to intervene, although in vain, on behalf of the Jewish chemist *Fritz Haber* (who had "deserved well of Germany")—but not in favor of the Jewish scientists within the Kaiser Wilhelm Society—when he paid his first visit to *Adolf Hitler*, which has often been mentioned[49]. *Hahn* reported these events[50]:

> "In the first instance *Haber* himself [sc. at the K.W.I. for Physical Chemistry and Electrochemistry] was not affected, but some excellent Jewish members of his staff had lost their posts. Some people who were members of the party or its organizations monopolized the situation and therefore *Fritz Haber* decided to resign from his post as head of his institute. In a letter to the new Minister of Education he declared that he did not want to be treated differently from his Jewish colleagues."

The reports from Berlin-Dahlem (probably from *Lise Meitner*) had made him break off his trip round America. In July he returned to Berlin, where *Planck* and *Haber* asked him to take temporary charge of *Haber*'s institute. *Haber* himself accepted an invitation to America, emigrated to England, and died on January 29, 1934, during a recreational trip to Switzerland. The courageous behavior of *Max Planck* and *Otto Hahn* in connection with the demonstrative commemoration they arranged for *Fritz Haber* on January 29, 1935, is well known[51]. Although the ceremony was not forbidden, the staff of universities, Kaiser Wilhelm Institutes and other associations were prohibited from attending the ceremony by decrees and official circulars. *Hahn* reported[52]:

> "In that grotesque situation *Planck* called for me ... at my institute. We did not know whether we should be hindered by force from entering the Harnack building. But nothing happened. Every seat in the beautiful hall was taken. The participants were a few relatives of *Haber*, but above all Geheimrat *Bosch* and leading men from the I.G. Farbenindustrie, whom *Bosch* had invited by telegram, many wives of the professors who were not allowed to attend at the ceremony, His Excellency *Schmitt-Ott*, Geheimrat *Willstätter*, who had come from Munich, and other close friends of *Haber*. In the back seats there were some members of my institute: *Lise Meitner*, *Fritz Strassmann*, *Max Delbrück*. The ceremony took a dignified and impressive course. Unfortunately Professor *Bonhoeffer* could not deliver his lecture himself. He would have lost his professorship at the university of Leipzig. At his request I read his lecture for him. I myself did not run any risk in the matter, because I had left the faculty in 1934 [correct: 1933] ... That commemoration of *Haber* shows that resistance (although only little) could still be offered during the first years of the Hitler regime, which later became impossible."

However, *Fritz Haber* had earned a great reputation by discovering the synthesis of ammonia and developing poison gas during World War I, and had been of inestimable service to German industry. *Max Planck* had also made that point to *Hitler*, and found the issue most perplexing for his attitude of mind was a rather traditional one of absolute loyalty to public authority[53]. As the "Permanent Secretary" of the Physical-Mathematical Class of the Prussian Academy of Sciences (1912—1938) and as the president of the Kaiser Wilhelm Society (1930—1937) he held positions that would have enabled him to engage in activities going beyond those demonstrations. What had been advantageous before 1933, when he succeeded *Adolf von Harnack* as president of the Kaiser Wilhelm Society in 1930—in addition to his tradition-bound

loyalty to the state which met the interests of business circles—now turned out to be a weakness[54]:

"It was good that the theologian was followed by the scientist *Max Planck* as head of a society with a primarily scientific alignment. It was desirable for the consolidation of the reputation of the Society in the international world that that post be taken by the greatest among the German physicists who was appreciated all over the world; it was necessary that the president not be one of the directors of the institutes, so that he could be both independent and authoritative towards them. But above all it was important that the president should have such a reputation that he spread an almost mythical magnificence around him, like *Harnack* had been known to do. This *Planck* did, although in a different way from that of his predecessor. While *Harnack*'s secret had been his superior gift of oratory, *Planck* was effective by virtue of his quietness and modesty, which raised him above the bustle of political circles, but often above that of the scientific ones too. Moreover, in particular he knew not only how to arouse respect but also love."

At this juncture, a younger and energetic man certainly could have better served the reputation of German science. When *Max Born* expressed his astonishment to *Max Planck* in July 1946 that he "didn't do anything for his Jewish colleagues", *Planck* could only quote his talk with *Hitler* concerning *Fritz Haber*[55]:

"I wonder whether *Max von Laue* would have signed in cases like that [*i.e.* exclusion of *Albert Einstein*, *Max Born*, and others from the Berlin academy], because his manner was more that of a hero and, unlike *Planck*, he was not so conservative that he would have obeyed the orders of the government even when they were bad."

Max Born was of the opinion that *Planck* had not been fainthearted, but that he had known "that any opposition would be in vain and dangerous for German science"—we can doubt that today, but we can neither prove nor disprove it. Too many people saw an unexpected chance for furthering their own personal careers by filling the gaps left by dismissal of Jewis staff, feared for their own fortunes, or were enthusiastic about the new national ideology with all its consequences and brutalities. And far more people thought that way than were ready to admit it later on, *i.e.* after 1938/39, and especially after 1945. *Otto Hahn*—the provisional head of *Haber*'s institute—at least tried to lobby for financial compensation for the Jewish colleagues who had been dismissed. On October 16, 1933, he wrote to his president[56]:

"Dear Geheimrat,
You ... charged me with the leadership of this institute. Now that my responsibility for the institute has come to an end, please permit me to refer once more to some points, the successful settlement of which seems important to me for political and human reasons ... They mainly concern a number of employees who were dismissed on the grounds of the law concerning Civil Servants [which pursuant to § 14 was accordingly applied also to employees], whose change to other livelihoods would be facilitated by severance pay ..."

So far, I have been unable to establish whether anything was undertaken by the presidency, but it is unlikely. Most probably *Hahn*'s efforts were largely due to *Lise Meitner*'s urgent requests. While *Hahn* had been well off as a student, had soon entered paid research work, and only came to know financial hardship for a brief time after the war—when everybody was suffering—*Lise Meitner*, of course, knew from experience what financial straits and need meant. Moreover, she had had to live on the initial salary of an assistant from 1938 to 1946/47, and life was expensive in Sweden. At any rate, *Lise Meitner* was the one who could induce *Otto Hahn* to grant the destitute *Fritz Strassmann* a support of RM 50 per month from mid-1934, taken from a private fund he had at his disposal for special contingencies. As *Strassmann* never talked much about his personal affairs—nor does he today—, his "boss" probably had not even realized his need. Indeed, the members of the staff of the institute never went to *Hahn* with their personal problems, but to *Lise Meitner*; and if he ever heard about such matters it was for the most part *Lise Meitner* who had told him. She was the true life and soul of the institute and her motherly care for the welfare of the members of her former staff—including those who had precipitated her departure at least by their behavior in 1938—is expressed in many of her letters to *Otto Hahn* from 1938 to 1947.

From the "Transuranics" to Uranium Fission (1934 to 1938): The "*Hahn-Meitner-Strassmann* Team"

Having gained his doctor's degree in physical chemistry under the supervision of *Hermann Braune*, *Fritz Strassmann* had been assistant at the Technische Hochschule of Hannover for a short time. With a rather modest scholarship granted by the "Notgemeinschaft der Deutschen Wissenschaft", he then came to the Kaiser Wilhelm Institute in the middle of 1929 in order to receive further training in radiochemical methods. Up to September 1932 the scholarship was prolonged twice. Thereafter he had to support himself by preparing students for their examinations, but he was allowed to continue his work in *Hahn*'s private Laboratory. His studies on (the refutation and modification of) "Hahn's emanation method" (1929—1934) had also earned him a reputation outside the institute. His knowledge and his skill at chemical analysis—*Otto Hahn* was the radiochemist and *Lise Meitner* was the physicist—predestined him as the necessary third man to join the *Hahn-Meitner* team when *Lise Meitner*, in the autumn of 1934 after more than ten years' break, succeeded in "persuading" *Otto Hahn* to embark on another joint study[57], *i.e.* the study of the alleged "transuranics", which *Enrico Fermi* and his collaborators had found by bombarding uranium and thorium with slow (so-called "thermal") neutrons. *Strassmann*, who had refused the offer of a lucrative post at Solvay A. G., thereafter repeatedly offered *via Hahn*, because his entering the firm would have meant his having to join a Nazi organization (a step he resisted until the collapse of the German Reich in 1945), was called on to join the team and was employed as assistant as of January 1, 1935[58].

It was only after *Lise Meitner*'s emigration that that teamwork led to the discovery of the fission of uranium nuclei by *Otto Hahn* and *Fritz Strassmann*.

All three always gladly remembered their collaboration between 1935 and 1938. Contrary to *Otto Hahn*'s statements—which make no mention of that detail among others—*Lise Meitner* was the intellectual leader of the team—at least in the eyes of *Fritz Strassmann*[59], who was the youngest member and the experimentalist of the group. As a witness to her authority, for instance, their signatures under announcements and directions on the bulletin board "*Otto Hahn, Lise Meitner*" were regularly "falsified" by a transposition mark into: "*Otto Hahn*, lies *Meitner*" (*i.e.* "read *Meitner*"). Her frequent saying: "Hähnchen, leave that to me, you have not the faintest notion about physics!" became almost proverbial among the staff. However, tacit acceptance of her authority also had negative consequences: *Strassmann* reports[60] that he had already found barium (instead of radium) on analyzing uranium irradiated with thermal neutrons one night in 1936 but *Lise Meitner*'s sceptical remark of the next morning, that that must be nonsense, had been sufficient for him to throw his records into the wastepaper basket without any regrets. *Hahn* heard nothing at all about that finding. In December 1938 it was precisely that result, which he had completely forgotten in the meantime, which confirmed his conviction that he had actually detected barium, whereas *Otto Hahn*, who wrote the text of the paper[61] without showing it to *Strassmann*, at that time still expressed himself very reservedly. Trying to analyze the parts played by *Lise Meitner* and *Otto Hahn* in their early joint work, *Werner Heisenberg* was certainly right, when he stated in his commemorative address (1968)[62]:

> "It seems to me that *Hahn* owed his success primarily to his qualities of character. His untiring energy, his unbandable industry in acquiring new knowledge, and his incorruptible honesty allowed him to work even more accurately and more conscientiously, to reflect on his own experiments with even more self-criticism, and to carry out even more controls than most of the other scientists who entered the new territory of radioactivity. *Lise Meitner*'s relation to science was somewhat different. She not only asked 'What', but also 'Why'. She wanted to understand ..., she wanted to trace the laws of nature that were at work in that new field. Consequently, her strength lay in the asking of questions and the interpretation of experiment. We may suppose that also in later joint work, *Lise Meitner* exercised a strong influence on the asking of the questions and the interpretation of the experiments and that *Hahn* mainly felt responsible for the thoroughness and accuracy of the experiments. However, that partition did not become obvious in their joint publications."

Yet there is no mention of *Fritz Strassmann*, who had supplied that component of analytical certainty which *Otto Hahn* did not have. Moreover, as a physical chemist he was the connecting link between the fields of the two older team members. *Heisenberg* also reported that when *Hahn* was later asked about *Lise Meitner*'s part in the discovery of uranium fission he was heard to say while enjoying a glass of wine[63]: "I don't know; I'm afraid Lischen would not have allowed me the fission of uranium." If he meant that *Lise Meitner* would not have published the results before they had been given a theoretical interpretation, he may have been right. Nevertheless, together with her nephew *Otto Robert Frisch*, while staying with relatives at Kungälv, she formulated the first correct interpretation of the chemists' experimental results as fission of the uranium nucleus immediately upon receiving a copy of the manuscript (December 30, 1938)[64].—The concept of *Bohr*'s "droplet model" of the atom provided the starting point[65].

Werner Heisenberg thus concluded: "So far one would be inclined to regard the fission of uranium as the ultimate triumph of many years of collaboration between the two scientists" (the name of *Fritz Strassmann* is again missing). But he revoked that conclusion, referring to the quoted remark of *Otto Hahn*[66]: "But perhaps that is not yet the whole truth." As long as he lived, *Otto Hahn* was reluctant to mention *Lise Meitner* in connection with the discovery of uranium fission, whereas *Fritz Strassmann*, the co-discoverer, is convinced that *Lise Meitner*'s part even up to the finding of the barium had already been so great that she must be ranked among the discoverers, not only because of the first correct theoretical interpretation. Other physicists would undoubtedly have reached that interpretation soon after the paper was published on January 6, 1939. *Strassmann*'s unconditional subordination to her authority in 1936 had subsequently given way to mutual respect between the physicist and the analytical experimentalist whose results she took seriously, even though they could not (yet) be interpreted theoretically. In her letters of 1938/39 she often stated her unconditional confidence in the results of the analyses which were inconceivable at the time because they contradicted the theory of physics. *Strassmann* remembers that it was precisely *Lise Meitner*'s objections to the first results and the suggestions she made in her correspondence with *Hahn*, which stimulated and inspired him in particular to reexamine again and again the products found first by *Irene Joliot-Curie* and *Paul Savitch* upon the bombardement of uranium by thermal neutrons. It was *Lise Meitner* who instigated those joint studies on the "transuranics"[67], and up to her departure in July 1938 she had experienced all the ups and downs, the knowledge of which was prerequisite for the discovery. Therefore she could also understand what was being done by *Otto Hahn* and *Fritz Strassmann* in the months after she had left, although *Hahn* hardly informed her about these matters in his numerous letters. She often expressed her regret at that. Presumably *Hahn* could not have given her more detailed information because the experiments were largely carried out autonomously by *Strassmann* alone (even up to the decisive indicator test)—that follows from the "Chemie II" notebook which is preserved at the Deutsches Museum (Munich). She only lacked the direct contact with the investigations; *Fritz Strassmann* still sensed her presence in the background. *Otto Hahn* described the close collaboration of the three scientists unconsciously differentiating between their contributions—realizing that two at a time would not have arrived at their results without their third companion—when he wrote at the end of their paper on the detection of barium, delivered on December 22, 1938[68]:

> "Because of the experiments briefly outlined, as chemists we ought to change the designations of the above scheme

and to insert the symbols Ba, La, Ce instead of Ra, Ac, Th [that was *Fritz Strassmann*'s point of view at that time]. As "nuclear chemists" closely connected with physics in a certain way we [*i.e. Otto Hahn*] cannot yet make up our mind to undertake that leap, which contradicts all previous experience of nuclear physics [*Lise Meitner*'s influence]. A number of strange coincidences might have feigned our results [*Otto Hahn*'s habitual cautiousness]."

Direct participation in the unequivocal identification of a first product of transformation of uranium nuclei bombarded with thermal neutrons, and thus the indisputable claim to being a co-discoverer together with *Otto Hahn* and *Fritz Strassmann*, was denied her owing to her departure, which was dictated by the circumstances prevailing at the time.

Escape from Germany

The situation described above had come to such a crisis in the spring of 1938 that *Otto Hahn* feared for the future of his colleague and tried to obtain an exit permit for her. Even within the institute, safety was no longer guaranteed[69]. The head of the guest department in the upper story of the institute at Dahlem, *Kurt Hess*, was a National Socialist hardly willing to make any concessions, whose "hope of inheriting the institute ... had become even greater after the events of 1933" *(Otto Hahn)*. There were other factors too. *Lise Meitner*—a "Jewess"—, *Otto Hahn*, *Max Delbrück*, and *Fritz Strassmann*—"politically stubborn" (*Strassmann* was later debarred from "Habilitation" for that reason)—brought the institute into disrepute, and that bad reputation also led to increasing discrimination within the Kaiser Wilhelm Society. The institute itself was divided[70]: "The representatives of the party, *[Kurt] Philipp* and *[Otto] Erbacher*, cut a great figure politically at that time and the rest had to hold back." *Gottfried von Droste* had joined the S.A. in 1933 and usually appeared in uniform; in 1938 he joined the N.S.D.A.P. too[71]. Apart from *Kurt Hess*, however, there seem to have been no human lapses towards *Lise Meitner*. Consequently, some members of her staff applied to her later in order to obtain a "Persilschein" during the denazification; she fulfilled such requests, though rather reservedly[72]. In 1963, when the post-war situation had returned to normal, she addressed the "Urania" at Vienna and talked about "Fifty years of physics", and finally on the years at Berlin-Dahlem[73]:

"... I must say that the years up to 1933 were very stimulating. We needed and we developed complicated apparatus in both departments, and we were surrounded by a crowd of young people, students and staff, who not only learned from us, but from whom we too could learn a great deal, as regards human relations and sometimes as regards our work. There was really a very strong feeling of solidarity between us, built on mutual trust, which made it possible for the work to continue quite undisturbed even after 1933, although the staff was not entirely united in its political views. They were, however, all united in the desire not to let our personal and professional solidarity be disrupted. This was a special feature of our circle and I continued to experience it as such right up to the time I left Germany."

Outside their own institute, however, the situation had changed. *Otto Hahn* recollected[74]:

"*Lise Meitner* had retained her position in the institute and there she was not disturbed at all, but she could no longer play any role in the scientific community outside and she could no longer go to the Physical Colloquy of *Laue*. Yet a change for the worse started after the annexation of Austria in early March 1938. The situation then became more difficult. At that time, according to *Graue*[75], *Hess* is said to have remarked: "The Jewess *[i.e. Lise Meitner]* endangers the institute." A report was also made to *Mentzel* (Ministry of Education) on her position, *etc.* Then I [*i.e. Otto Hahn*] too rather lost my nerve and in a conversation with *Hörlein* (our treasurer[76]) I spoke of *Lise Meitner* and the new awkward situation since the annexation of Austria. *Hörlein* suggested that *Lise* might resign from her position, because nothing more could be done; perhaps she could continue working inofficially. I do not exactly remember the concrete proposals. Unfortunately I told *Lise* about that conversation on March 22, 1938... *Lise* was very unhappy and angry with me, because now I had also let her down... I do not remember in detail what happened later. The president *Bosch*[77], who spoke to Dr. *Telschow*[78] with regard to *Lise*, objected resolutely to *Hörlein*'s proposal: it would be alright for her to stay... The situation became more and more unbearable. *Lise* was very angry with me and could not get over my having spoken about her to *Hörlein*. On the other hand I was continually being told that *Lise* ought to have given up her post long ago, because she ought to see that she endangered the institute *etc.* ..."

Carl Bosch then had a rather long talk with *Lise Meitner* and they agreed that in the existing situation—the Ministry had been informed, events had been set in motion, although unintentionally, by *Otto Hahn*'s genuine concern—an official application for an exit permit would be the most reasonable course of action. On May 20, 1938, he submitted to the Reichsminister the written request "to permit the famous scientist Professor *Lise Meitner* to leave for a neutral foreign country, Sweden, Denmark, or Swizerland"[79]. In order to prevent any danger to the person of *Lise Meitner* by measures that might possibly be triggered by that request, she had taken up residence at the "Adlon Hotel". *Max von Laue* had reported that he had heard of an order issued by *Heinrich Himmler*, that no university scholars—whether Jews or not—would be allowed to leave Germany in the future[80]. The answer of the Ministry of June 16, 1938, to *Carl Bosch* turned out accordingly. He advised *Lise Meitner* of it by telephone, and she took it down in shorthand[81]:

"Dear Geheimrat *[Bosch]*!
By order of the Reichsminister Dr. *Fr[ick]* may I most respectfully inform you in answer to your letter of the 20th of last month that there are political objections to the issuing of an Auslandspass [*i.e.* a passport for traveling abroad] to Prof. *M[eitner]*. It is considered undesirable

that renowned Jews [underlined!] should leave Germany for abroad to act there against the interests of Germany according to their inner persuasion as representatives of the German sciences or even with their reputation and experience. The K. W. G. will certainly find a way for Prof. *M[eitner]* to stay in Germany after her retirement and under certain circumstances [...] The Reichsführer-SS and Chief of the German Police in the Reich Ministry of the Interior *[i.e. Heinrich Himmler]* in particular has advocated that opinion.

Yours respectfully"

A retreat now seemed to be impossible without endangering *Lise Meitner*. The forfeiture of her post seemed inevitable, although *Carl Bosch* still intended to intervene directly with *Himmler*[82]. However, events overtook that intention. Immediately after the official reply quoted above, *Otto Hahn* and his friend *Paul Rosbaud*, whose political attitude (at the same time he sent his family to England) and capacity as scientific adviser to the Springer Verlag and actual editor of "Die Naturwissenschaften" had earned him many friends abroad, took pains to arrange *Lise Meitner*'s illegal emigration and a way in which she could continue her work in an institute abroad. Whether she knew all about those endeavors or not, does not follow from the records and letters available until now. Later, however, she felt as if she had been sent away by her friends; only on the evening before her departure had they hastily packed a few things in a suitcase. Through the intervention of *Peter Debye*, at that time director of the Kaiser Wilhelm Institute for Physics at Berlin, their efforts were soon rewarded. Coming from Holland himself, he got in touch with his colleague *Dirk Coster* from Groningen, who was able to arrange that *Lise Meitner* would be allowed to enter Holland at a small frontier crossing without a valid passport and without an entry visa. *Dirk Coster* sent a telegram saying that he would come to Berlin in person. He arrived at Berlin-Dahlem on the evening of probably 13th or 14th July[83]:

"*Coster* stayed in Berlin for a night. Without telling anybody, a suitcase was packed in the evening (only *Rosbaud* and I *[i.e. Otto Hahn]* were present). As far as I remember, she spent the night before her departure with us at the Altensteinstrasse; *Coster* himself only met her in the train. Then they left; with fear and trembling we wondered whether she would get through or not" ... "We had agreed upon a code word by which we were to be informed by telegram on the success or failure of the journey. *Lise Meitner* was especially exposed to the danger of repeated controls by the SS in the trains going abroad. Time and again, people who tried to go abroad had been arrested on the trains and brought back. But *Lise Meitner* was lucky; she got across the border and was safe."

On July 15, *Otto Hahn* could confirm receipt of the news of her safe arrival at Groningen by an encoded postcard[84]:

"Dear Coster family,
First of all I want to congratulate you on the happy arrival of the youngest member of your family. Of course, I was very pleased about the news, since we had been rather worried recently. What will be the name of your darling daughter?—There is not much news here. In the laboratories everything takes its usual course, and vacation starts tomorrow, thank goodness..."

The staff and outsiders thought that *Lise Meitner* was on vacation. That was not suspicious, because the general vacation of the institute started on July 16. Of course, she remained "Wissenschaftliches Mitglied" of the Kaiser Wilhelm Society and head of the physical-radioactive department of the institute. Her contract had been renewed by the Kaiser Wilhelm Society in 1929, being back-dated to April 1, 1928, in order to supplement it by the extension of her status to that of a life employee entitled to the pension of a ordinary professor. Therefore the wording of a letter of the Reich Ministry of Education of August 11, 1938, to the General Administration of the Kaiser Wilhelm Society is all the more peculiar. The formulation was based on a consultation between *Rudolf Mentzel*, the Referee for Sciences and Technology in the ministry, who had also been president of the "Deutsche Forschungsgemeinschaft" since 1936 (succeeding *Johannes Starck*) and consequently permanent member and real "leader" of the Reichsforschungsrat founded in March 1937[85], and the director of the General Administration of the Kaiser Wilhelm Society, *Ernst Telschow*. The letter reads as follows[86]:

"Re: Frau Professor *Lise Meitner*.
Professor *Lise Meitner*, previously an Austrian national, is working as a guest [?] at the Kaiser Wilhelm Institute for Chemistry. Since she has become a German national through union with Austria, it has to be established what percentage of Jewish blood she has. According to previous assessments Mrs. *Meitner* is supposed to have 25 % of Jewish blood.
Referring to the talk which my referee Professor Dr. *Mentzel* had with Dr. *Telschow*, I ask for prompt comment on that matter.

By order,
signed *Dames*"

Thereupon *Ernst Telschow* wrote to the director of the Kaiser Wilhelm Institute for Chemistry, *Otto Hahn*, on August 18, 1938[87]:

"Dear Professor *Hahn!*
I enclose a transcript of a decree of the Reich Ministry for Education [the letter above] for your information. You may discuss the matter with Prof. *Meitner* and inform me about what is necessary for the reply to the Ministry. I suppose that—now that the Ministry has taken up the affair—it would be expedient if Mrs. *Meitner* were herself to apply for leave until the question of her retirement or staying at the Kaiser Wilhelm Society will be cleared up. Such an application would certainly be of use for the future discussion with the Ministry.

Heil Hitler!
Yours faithfully, *Telschow*."

"Taking everything into account", *Otto Hahn* did not inform *Lise Meitner* about that letter; he "thought, you *[i.e. Lise Meitner]* would have preferred to reach your decision without

being influenced"[88]. And, indeed, without knowing about the letter she wrote to him on August 24, 1938[89]:

"Dear *Otto*,
What I have to tell you today will bring about an extremely decisive turning-point in both our lives. Yesterday I asked Geheimrat *Bosch* to agree to my retirement.
We need not speak about feelings, both of us certainly know about such things. I am sure no day will pass, when I shall not think with gratitude and longing of our friendship, our joint work, and the institute. But I don't belong there any longer, and when I reflect on the last months, it seems to me that my retirement will also comply with the wishes of the staff. It's no use talking about it too much; facts are facts, you cannot pass them over.
My Swedish friends offered to let me stay with them, and I have come to the decision that this is the only course left open to me. Actually I would like to express my thanks personally to all the colleagues and employees of the institute for the years of excellent cooperation. But perhaps you think it would be better you alone were to tell them. They all know me, well enough to know that I don't like talking about things that are irrevocable. Think it over calmly and let me know which form you consider suitable. However, please let's not talk about the fact of my leaving.
Of course, my decision involves a number of practical necessities. I also wrote a very short letter to Dr. *Telschow* and asked him to discuss the regulation of my affairs, such as retiring allowance *etc.* with Dr. *Leist*. I'll ask *Annchen* to carry out the dissolution of my flat, with the help of a removal company, of course. I know very little about the legal formalities but I hope for the help of Dr. *Leist*. I have not yet made any detailed plans, I just thought that I would put my things in storage here. And then I must await what the future brings. I also need inner calm to think over everything rationally.
In my inner self I myself have not yet quite realized that what I have just written is real, but it *is* real.—Let me hear from you soon. With very kind regards,
Yours forever,
Lise."

In Swedish Exile

Lise Meitner had meanwhile left for Sweden, with the help of *Peter Debye* and of *Niels Bohr*, who had been her friend since 1920. *Niels Bohr*, who after World War I had already made unparalleled efforts to ensure German scientists should regain recognition abroad, had also started in 1932/33 a worldwide campaign to provide Jewish scientists persecuted by the Nazi regime with posts in foreign institutes. After *Hitler*'s seizure of power he had traveled around Germany officially in order to "visit German universities", but actually in order to gain first-hand knowledge about the effects of the race laws[90]. He procured positions for many people at English, American, Dutch, Danish, Swedish, *etc.* institutes; *e.g.* he had invited *Otto Robert Frisch*, a young physicist from Hamburg and nephew of *Lise Meitner*, who had spent some time with *Patrick Blackett* in London, to his own institute at Copenhagen. For *Lise Meitner*, who would have had entirely different prospects in 1933 at the onset of *Bohr*'s campaign, they had obtained a place to work at *Manne Siegbahn*'s Nobel Institute for Physics, recently founded at Stockholm. Therefore at the end of July 1938 she went to live with her friend *Eva von Bahr-Bergius* at Kungälv near Gothenburg (whence she sent her farewell letter, quoted above), and in mid-September she moved into a small hotel room in Stockholm, where in May 1939 together with some relatives she occupied a flat—for the time being without her belongings, however, the transport of which from Berlin was proving difficult[91].

The working conditions at Stockholm, however, did not come up to all the hopes and expectations raised by *Debye*'s information. Some passages from postcards and letters to *Otto Hahn* illustrate her first disappointment and her situation[92]:

"25/VII '38 ... My journey to her *[Eva von Bahr-Bergius]* could not be arranged yet. *Manne [Siegbahn]* did not quite understand what I am particularly interested in; I have written to him once again [...] 26/VII: Now it seems, that I'll be leaving after all during the next few days. So please write to *Eva*'s address."—"25/IX '38 ... Perhaps you cannot fully appreciate how unhappy it makes me to realize that you always think that I am unfair and embittered, and that you also say so to other people. If you think it over, it cannot be difficult to understand what it means to me that I have none of my scientific equipment. For me that is much harder than everything else. But I am really not embittered—it is just that I see no real purpose in my life at the moment and I am very lonely..."—"6/XI '38 ... On Monday (12th) *Bohr* will deliver a lecture here. I hope I can speak to him a little on his own. *Siegbahn*'s institute is incredibly empty. An excellent building where preparations are being made for a cyclotron and many other large X-ray and spectroscopic apparatus; but experimental work can hardly be *thought* of. There is no pump, no rheostat, no capacitance, no ammeter—*i.e.* nothing for doing experiments, and in the entire building just 4 younger (or young) physicists and very bureaucratic working rules ..."—"15/X '38 ... There is little to tell [from here]. Experimental work is out of the question; it will take a very long time until even the simplest apparatus will be there, and then perhaps also a collaborator. Of course, *Bohr*'s visit was very pleasant and probably useful, too, because he also spoke to *Manne S[iegbahn]*. But *S[iegbahn]* is not at all interested in nuclear physics and I rather doubt whether he likes to have an independent person beside him. *B[ohr]* suggested that I should have patience, what else should he do. And I can't do anything but live my life just as it is..."—"26/XI '38 ... Your suggestions for the apparatus are hardly practicable. It would be so much better, if one could come to *Siegbahn* so to speak with a gift instead of a demand, and if it were only a drawing of a piece of apparatus. However, that doesn't seem possible ..."—"5/XII '38 ... There is little or nothing to tell about myself ... I often feel like a wound-up puppet that does certain things, gives a friendly smile, and has no real life in itself. By that you can judge how valuable my activity is. Nevertheless, I am very grateful for it after all, because it compels me to collect my thoughts, which is not always easy ..."—"21/XII '38 ... As for my so-called work—when I think it over—I can only think and say,

o God! I have set up a single-filament electrometer, some counters, an amplifier, a very poor counter, no help whatever. Mostly my head is really so full of other matters that the rest is all the same to me. Nevertheless, life must be lived in some way or other ..."—"14/I '39 ... It is certainly nice that *Siegbahn* is getting the counter. Once more, he didn't tell me a word about it, I finally asked him. It's all very depressing, but I don't see any possibility of changing things. ..."—"25/I '39 ... If you could but see my day's work! I have *no* help at all, I cement counters, evacuate them, test whether they are leakproof, in short I do the work of Mr. *Dörf[f]el* [technician at the Kaiser Wilhelm Institute at Berlin], only much worse than he does ..."—"5/II '39 ... I don't feel at all happy. Here I just have a workplace no position that would entitle me to anything. Try to imagine what it would be like if, instead of your nice private institute, you had a room in an institute which is not your own, without any help, without any rights and with the attitude of *Siegbahn* who only loves big machines and who is very confident and self-assured—and there am I with my inner shyness and embarrassment! And that I have to do all the petty work which I haven't done for 20 years. Of course, it's my fault; I should have prepared my departure much better and much earlier, I should at least have had drawings of the most important apparatus *etc. Siegbahn* also once told me that *Debye* hadn't written anything about collaborators or assistants (several times I had asked *D[ebye]* for that) and that he had only little room. Yet, that's not true, I think. But the essential thing is that I have come here so empty-handed. Now *Siegbahn* will soon believe—especially after your excellent results—that I didn't do anything and that you both did all the physics too at Berlin Dahlem, Gradually, I am losing all my courage ..."—"12/II '39 ... As for *Debye*, it was he who wrote (July 1938) to *Manne* and obviously he didn't mention anything about co-workers or an assistant ... I have really done everything wrong that could be done wrong. And, in addition, I started from completely wrong premisses. Meanwhile, I have gradually come to know through *Eva von B[ahr-Bergius]* what happened. *Siegbahn* didn't really want me. He said that he had no money; he could give me a place to work but no more. *Eva* then wrote to *Oseen*, and he said that the Nobel foundation could grant money. But no one considered that I can't work without an assistant, especially in an institute where there is nothing available for my field. And when I realized that, I was rather desperate, and that, of course, isn't the right state in which to assert oneself. At Dahlem I used to talk the matter over with *Gille*, when I needed something from the workshop, and he did the mechanical work and also produced the drawings. Here I'm always told: "Make a drawing, please." That means, I do the work which *Dörf[f]el* had done and, strictly speaking, I don't know to do it. And *Siegbahn*, who is a wonderful draftsman and technically highly gifted, will now soon think that I know nothing at all. Perhaps he is right ... I shouldn't have left in such a way; on the contrary I should have had drawings of the most important apparatus ..."—"31/III '39 ... Probably you can't really imagine what it means for a person of my age to have been living in a small hotel room for 9 *months*, without any comfort, without any scientific aids, and with the fear that nobody has the time required to advance my affairs [at Berlin] ... And here in the institute, too, I'm without any help, and I don't think that *Siegbahn* is much inclined to assist me in it ... I found the counter when I came back [from a 4-week stay at *Bohr*'s institute at Copenhagen, which made her perceive even more strongly her situation[93]], and I tried it today, it's all right ..."[94]—"27/X '39 ... My work is equivalent to zero ..."—"12/XI '39 ... The young physicist from Utrecht who wanted to come here wasn't given a Swedish entry visa, we don't know why, and *Manne*, who at first wanted to lend a helping hand, told me some 2 weeks ago that there would be no sense in trying[95]. In principle he may be rather glad that it turned like that. He much prefers to spend the funds of the institute on mechanics and big machines than on scientists and scientific problems. In the whole institute there are only 5 scientists, and even they work almost exclusively on apparatus. Scientifically I'm completely isolated, I don't talk with anybody about physics for months, I'm sitting alone in my room trying to occupy myself; it can't be called "work" ..."—"20/VIII '40 ... That you didn't inform me about the result before the paper was ready for the press, shows to me how much you overrate my facilities and how much you underrate my colleagueship. A pity! ..."—"14/XI '40 ... Unfortunately, within the next few weeks the assistant who is building the cyclotron will go to Upsala, where he'll have a permanent position; Heaven knows what's going to happen about the cyclotron. Particularly sad is *Norling*'s recent sudden death ..., he had worked with *Bothe* for more than a year, he was greatly talented and really interested in nuclear physics and as a person he was such a nice boy ..."—"20/I '41 ... *Manne [Siegbahn]* suggested that I give some lectures in the institute for him and his young people "in order to show them what problems are experimentally solvable". Of course, it's a bit naive to think that you can learn to work independently in a new field by a few lectures, but still the very insight that there is something they can learn from me is progress (reached after several years). And for myself it's good to be compelled to think over the field once again more thoroughly ..."—"15/VI '41 ... My facilities are becoming more and more limited because the problems that can be treated with such a weak neutron source and without any help are very few in number ..."—"3/IX '41 ... Since the beginning of August I'm back and at work, in so far as my rather modest occupation deserves to be called work. This institute is really unique. For three years various apparatus have been built—I have not yet seen a finished one—but problems are not dealt with, except by *Norling*, who unfortunately died a year ago. Once *Manne [Siegbahn]* asked me to help his son prepare a ThB preparation with which a β-spectrograph should to be tested—I heard of its existence then for the first time. Of course, I did so, but when I asked about the results some time later I got an evasive answer, and so far as I know nobody is working with it any longer. The cyclotron is standing around unfinished, lonely and forsaken ..."—"22/X '41 ... Lately I have—*faute de mieux*—worked a little on γ-rays and Compton electrons and I have come across problems of the sensitivity of counters, like those *Droste* dealt with in the year 1938. There would

be a lot to discuss about that, but as I haven't heard anything at all of him, there is no point in asking questions ..."—"26/II '42 ... My life is so empty that there is really no point in saying anything about it. If I had the gift of regret, I would never get over the fact that I returned to Stockholm several years ago [probably after her longer stay at Cambridge]. But there is no use in occupying oneself with that. The cyclotron has been working for several weeks, but irradiation is done only for *Manne [Siegbahn]*, ... and no neutrons are produced in the cyclotron, but deuterons are used directly for activation, *i. e.* the sample to be activated must be placed into the cyclotron; so there is no room for anything else. I don't know how long it will go on like that ..."—"30/XII '42 ... Your wishes for a "successful year" sound almost like irony, which of course you hadn't intended. But if you knew my working conditions! Recently I asked *Manne* whether I could occasionally get something irradiated, whereupon he took out his notebook and said: "Which day? All the work is under my control, you know ..." He doesn't like the young people and myself talking to each other, but nevertheless they do talk to me and consult me. But I suppose you will understand that one can't really work, if one can't try out what one has thought of with any modifications that may be necessary."—"12/IX '43 ... There is not much to tell about my work, as always it's going very slowly. Nevertheless, for 4 weeks I have a young electrical technician working with me, who seems to be qualified and humanly sympathetic. Let's hope for the best ..."—"15/XI '43 ... Dr. *[Sigurd] Eklund*, assistant to *Siegbahn*, urgently needs anhydrous (*i. e.* fused) boron trioxide, but he can't get it here. Could you have 250 g sent to him—on payment, of course? I would be pleased, if it were possible, he is always so ready to alleviate my unfavorable working conditions, so it would be nice, if I could help him in return ..."—"22/IV '44 ... Work is progressing slowly, and it is sometimes also difficult to focus one's thoughts on it. If only the world would but get out of this hubbub! ..."—"21/VI '44 ... One can think of hardly anything but current events. Everything else has become so unimportant, even the scientific work sometimes appears completely pointless to me. Together with my assistant I have been building up a coincidence set-up, which is almost finished. It was so difficult to get the necessary components, especially the amplifier tubes. In Sweden they don't produce any tubes, therefore we are completely dependent upon foreign tubes, and those are hardly available ..." [*Otto Hahn* then sent her two tubes, which, however, never arrived at Stockholm.]

In 1947 *Lise Meitner* retired from the "Forskninginstitutet för Fysik" of the Swedish Academy, after she had spent six months of 1946 as visiting professor at the Catholic University of Washington, D.C., in the United States, where she was nominated "Woman of the Year" by the American press and received honorary doctorates from several universities. The Swedish Atomic Energy Committee had offered to set up a small laboratory for her at the "Försökstation" of the "Ingeniörs-Ventenskapsakademien" at the Royal Institute of Technology at Stockholm, to which she moved at the beginning of 1947. Connected with the laboratory position was the post of a research professorship, the granting of which by the Swedish Parliament nevertheless dragged on for some time. On March 30, 1947, she wrote to *Otto Hahn*[96]:

"I'm to get a research professorship at the Royal Institute, *i. e.* without teaching obligations, but also without an institute or other rights. But the professorship has not yet been passed by parliament. The Ingeniörs Vetenskapsakademie (Professor *Velander*) has set up 3 very small rooms for me in its Försökstation, *i. e.* I have money for the simplest apparatus, voltmeters, ammeters, amplifier tubes, *etc.*, which I am now trying to buy, and I have 2 assistants, a purely technical one and a young engineer, neither of them has any idea of nuclear physics. At the Försökstation a Van de Graaff is being projected, maybe it will be built in 2 years, and a small high voltage installation is being built (smaller than the one *Bosch* had granted to me[97]). Of course, a cyclotron is no longer under discussion, and *Siegbahn* will now be even less willing to have anything irradiated for me ..." And on 24/VI 1947[98]: "... My post at the Royal Institute has come to nothing, despite all the promises the motion wasn't brought before parliament, and *Jacobssen* recently rang me up and tried to prepare me that it would probably come to nothing at all. If *Borelius* hadn't taken care of it at the end of May, there wouldn't have been any salary for me on and after July 1. Now it will be granted for another 6 months [by the Nobel Foundation] ..."

But also that problem was solved at the end of 1947; for on March 4, 1951, when the question of *Lise Meitner*'s retirement salary (a transfer of which hadn't been approved in 1938, but which for some months had been paid to her sisters at Vienna—who had lost their posts, too—up to their flight) was finally settled by the Max Planck Society, the legal successor of the Kaiser Wilhelm Society, she wrote to *Otto Hahn*[99]:

"In regard to the retirement pay awarded to me by the K.W.I. [*i. e.* K.W.G.] I had thought of a short visit to Germany, you know ... But now the Max Planck Soc[iety] tells me that I should specify my salary drawn here at present, which should be set off against the retirement pay. At the moment I have a rather high salary, having had not even the starting salary of a assistant for 9 years ..."

At the end of 1953 she gave up the laboratory at the Försökstation of the Institute of Technology and got "a sort of advisory post at the institute of *Eklund* ..., rather in order to have a room and a library at my disposal, that means a sort of "Altersstübel" [room set aside for an old person]"[100]. *Sigurd Eklund* was then building a research reactor for the Royal Academy of Engineering deep down in a cavern under Stockholm. He and *Lise Meitner* had been friends since the time spent together at *Siegbahn*'s institute, when he had been the only person who cared a little for her.—In 1960 *Lise Meitner* moved to Cambridge, where relatives (among others her nephew *Otto Robert Frisch*) were living, in order to be nearer to them in her old age. There she died on October 27, 1968, shortly before her 90th birthday—and only a few months after her old "companion" *Otto Hahn*.

Late Appreciation of the "Joint" Discovery of Uranium Fission: The Enrico Fermi Award

In her old age it was of little comfort that in 1966, after many other decorations and honors, she was awarded, together with *Otto Hahn* and *Fritz Strassmann*, the Enrico Fermi Award (granted "for especially meritorious contributions to the development, use, or control of atomic energy") of the President of the U.S.A. and the United States Atomic Energy Commission, "for contributions to nuclear chemistry/physics and extensive experimental studies culminating in the discovery of fission"—not because her age prevented her from undertaking the journey to Vienna, where because of her the ceremony had been held instead of Washington, D.C., but rather because *Otto Hahn*, who had already received the Nobel prize for chemistry of 1944 for that discovery[101], was awarded that prize, too, and because the shares of the three "discoverers" up to the discovery and interpretation of the nuclear fission would first be acknowledged so late by the public, because she had had to leave Germany previously and *Otto Hahn* by supplying insufficient information and hasty publication had deprived her of the chance of also contributing her share to that paper on the discovery of the fission products? But that is speculation. However, as far as *Fritz Strassmann* was concerned she was really pleased. Be that as it may, being informed of the award for the prize she wrote in a postcard to *Hahn*[102]:

> "The granting of the Enrico Fermi Award to you, *Strassmann*, and me comes as a great surprise to me, about which I'm really glad for both of you. As for my part, my feelings are rather mixed. However, in some respects I'm sort of pleased about it, too ..."

What would she have said, if she had known—as probably hardly anyone knows even today—that it had been *Otto Hahn* himself whose proposals had led to the granting of the award to the three discoverers of nuclear fission. The General Advisory Committee of the United States Atomic Energy Commission had invited him to nominate a candidate for the award—for the first time at the beginning of 1963, and for the second time on January 9, 1964 (the prize was not awarded in 1965). On both occasions *Hahn* had nominated *Fritz Strassmann* alone[103]—and that would certainly have completely reconciled her.

This paper could not have been written without the help of many people whom I interviewed or asked for sources during my research work in the archives. Among others I am very much obliged to Mrs. Patricia Bradford, archivist of Churchill College at Cambridge, Mrs. Marie-Luise Rehder, the long standing secretary and trustee of the literary estate of Otto Hahn, Mrs. Hildegard Scheld, the librarian of the Max Planck Institute of Chemistry (Otto Hahn Institute) at Mainz, Mrs. Ursula Ringmann from the personnel division of the General Administration of the Max Planck Society at Munich, Dr. Rolf Neuhaus, the director of the Library and Archives for the History of the Max Planck Society in Berlin, my friend Robert S. Westman, Ph.D., at present at Cambridge, and above all Prof. Otto Frisch, Cambridge, and Prof. and Mrs. Fritz Strassmann, Mainz. In translating I was helped by Miss Ingrid Roegner.

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[1] See *A. Hermann:* Max Planck in Selbstzeugnissen und Bilddokumenten. Rowohlt, Reinbek 1973 (rowohlts monographien, 198), p. 91.
[2] *O. R. Frisch, F. A. Paneth, E. Laves, P. Rosbaud:* Beiträge zur Physik und Chemie des 20. Jahrhunderts. Lise Meitner, Otto Hahn, Max von Laue zum 80. Geburtstag. Vieweg, Braunschweig 1959. In English: Trends in Atomic Physics. New York: Wiley-Interscience, New York 1959).
[3] See *A. Hermann:* Die Jahrhundertwissenschaft. Werner Heisenberg und die Physik seiner Zeit. Deutsche Verlagsanstalt, Stuttgart 1977; *K. Mendelssohn:* Walther Nernst und seine Zeit. Verlag Chemie, Weinheim 1976.
[4] *F. Strassmann*, "Zur Erforschung der Radioaktivität. Lise Meitner zum 75. Geburtstag", Angew. Chem. *66*, 93 (1954).
[5] *E.g. O. Hahn*, a) "Lise Meitner 70 Jahre", Z. Naturforsch. *A 3*, 425 (1948); b) "Lise Meitner 80 Jahre. Zum 7. 11. 1958", Naturwissenschaften *45*, 501 (1958); c) "Lise Meitner 85 Jahre", *ibid. 50*, 653 (1963); *Elisabeth Schiemann*, "Freundschaft mit Lise Meitner", Evangelische Frauenztg. *3*, Issue 1 (1959).
[6] In most detail and with bibliography *O. R. Frisch*, a) "Lise Meitner, 1878—1968, Elected For. Mem. R. S. 1955", Biogr. Mem. Fellows R. Soc. *6*, 405 (1970); b) "Meitner, Lise" in: Dictionary of Scientific Biography, Vol. 9. Ch. Scribner's Sons, New York 1974, p. 260; c) "Distinguished Nuclear Pioneer—1973: Lise Meitner", J. Nucl. Med. *14*, 365 (1973).—Cf. also *F. Strassmann*, "Lise Meitner 7. 11. 1878—27. 10. 1968", Mitt. Max-Planck-Ges. *1968* (Issue 6), 373; *W. Heisenberg*, "Gedenkworte für Otto Hahn und Lise Meitner", Orden pour le mérite für Wissenschaften und Künste: Reden und Gedenkworte *9*, 111 (1968/69); *B. Karlik*, "Gedenkworte für Lise Meitner", in: Akademische Gedenkfeier zu Ehren von Otto Hahn und Lise Meitner am 21. Februar 1969 in Berlin. MPG, München 1969.
[7] For biographical information, cf. in addition to *O. R. Frisch* [6a, b], especially the autobiographically oriented sketches by *L. Meitner* (a) "Looking Back", Bull. At. Sci. *20* (No. 11), 2 (1964); Adv. Sci. *20*, 39 (1964); b) Einige Erinnerungen an das Kaiser-Wilhelm-Institut für Chemie in Berlin-Dahlem. (Otto Hahn zum 75. Geburtstag am 8. März 1954)". Naturwissenschaften *41*, 97 (1954); c) "Max Planck als Mensch", *ibid. 45*, 406 (1958).
[8] *F. Strassmann* in [4], p. 94.
[9] *O. R. Frisch* in [6a], p. 405; *L. Meitner* in [7a], p. 2.
[10] *L. Meitner* in [7a], p. 3.—Concerning the Viennese physical institute at that time, cf. *K. Przibram:* Erinnerungen an ein altes physikalisches Institut, in [2], pp. 1—6.
[11] *L. Meitner*, "Über die Absorption der α- und β-Strahlen". Phys. Z. *7*, 588 (1906).
[12] *L. Meitner* in [7a], p. 5.
[13] *A. Kirchhoff:* Die Akademische Frau. Gutachten hervorragender Universitätsprofessoren, Frauenlehrer und Schriftsteller über die Befähigung der Frau zum wissenschaftlichen Studium und Berufe. Berlin 1897.
[14] *M. Planck* in [13], pp. 256sq. (italics by the author); facsimile in *A. Kleinert*, "Vom Trieb zur theoretischen Physik. Eine Stellungnahme Plancks zur Frage des Frauenstudiums", Phys. Bl. *34*, 31 (1978).
[15] See *L. Meitner* in [7c].
[16] *L. Meitner* in [7a], p. 5.
[17] See *O. Hahn:* Vom Radiothor zur Uranspaltung. Eine wissenschaftliche Selbstbiographie. Vieweg, Braunschweig 1962, p. 37 sqq.
[18] *L. Meitner* in [7a], p. 5.
[19] See ref. [18].
[20] Archives of the Max Planck Society, Berlin (literary estate of Otto Hahn), and Archives of Churchill College, Cambridge (Meitner papers).
[21] Archives of Churchill College, Cambridge (Meitner papers).
[22] See ref. [20].
[23] See *O. Hahn* in [17], p. 59 sqq.
[24] *O. Hahn, Lise Meitner*, "Über die Absorption der β-Strahlen einiger Radioelemente", Phys. Z. *9*, 321 (1908); and other papers; cf. the bibliography of *L. Meitner*'s papers by *O. R. Frisch* in [6a], pp. 416—420.
[25] See *O. Hahn* in [17], pp. 52—56.
[26] 25 Jahre Kaiser-Wilhelm-Gesellschaft zur Förderung der Wissenschaften. 3 Vol., J. Springer, Berlin 1936; 50 Jahre Kaiser-Wilhelm-Gesellschaft und Max-Planck-Gesellschaft zur Förderung der Wissenschaften, 1911—1961. Beiträge und Dokumente. Göttingen 1961; *F. Glum:* Zwischen Wissenschaft, Wirtschaft und Politik. Bouvier, Bonn 1964; *L. Burchardt:* Wissenschaftspolitik im Wilhelminischen Deutschland. Vorgeschichte, Gründung und Aufbau der Kaiser-Wilhelm-Gesellschaft zur Förderung der Wissenschaften. Vandenhoeck u. Rupprecht, Göttingen 1975.
[27] See *L. Meitner* in [7b], p. 98, and [7a], p. 6.

[28] *O. Hahn, Lise Meitner*, "Die Muttersubstanz des Actiniums, ein neues radioaktives Element von langer Lebensdauer", Phys. Z. *19*, 208 (1918); cf. "Notiz über die Entdeckung des Protaktiniums", Naturwissenschaften *19*, 738 (1931).

[29] *Lise Meitner*, "Die γ-Strahlung der Actiniumreihe und der Nachweis, dass die γ-Strahlen erst nach erfolgtem Atomzerfall emittiert werden", Z. Phys. *34*, 807 (1925).

[30] *Lise Meitner, K. Philipp*, "Die Anregung positiver Elektronen durch γ-Strahlen von ThC''', Naturwissenschaften *21*, 468 (1933).

[31] See above [22] the letter to *Otto Hahn* dated June 6, 1948.

[32] Cf. *E. Boedeker:* a) Marksteine der deutschen Frauenbewegung von ihren Anfängen im 19. Jahrhundert bis zum Neuanfang nach 1945. Published by author, Hannover 1968 (^{3}1973); b) 25 Jahre Frauenstudium in Deutschland. Verzeichnis der Doktorarbeiten von Frauen von den Anfängen bis 1933. 4 Issues. Verlag Trute, Hannover 1935—39 (here Issue 1).

[33] *E. Boedeker, M. Meyer-Plath:* 50 Jahre Habilitation von Frauen in Deutschland. Eine Dokumentation über den Zeitraum von 1920—1970. O. Schwartz, Göttingen 1974 (Schriften des Hochschulverbandes, 27).

[34] Zentralblatt für die gesamte Unterrichtsverwaltung in Preussen, Jg. 1920. p. 240; see also in [33], p. 5.

[35] It was not before the end of World War II that women once more took "Habilitation" examinations in physics: *Iris Runge* at Berlin (Humboldt University) in 1947, *Liselott Herfort* at Leipzig in 1954, *Katharina Domberger-Schiff* at Berlin (Humboldt University) in 1954, *Erika Böhm-Vitense* at Kiel in 1959; for others see in [33], p. 176 sq.—Generally, see also *C. Lorenz:* Entwicklung und Lage der weiblichen Lehrkräfte an den wissenschaftlichen Hochschulen Deutschlands. Duncker & Humblot, Berlin 1953.

[36] See *O. R. Frisch* in [6a], p. 408.

[37] Reichsgesetzblatt 1933, Teil I, Nr. 34, of April 7, 1933, p. 175 sqq.

[38] Cf. now *A. Hermann* in [3], pp. 112—147.

[39] Cf. Zur Situation der weiblichen Hochschullehrer. Vorträge auf der Tagung des Deutschen Akademikerinnenbundes vom 7. bis 11. Oktober 1962 in Bad Godesberg. O. Schwartz & Co, Göttingen 1963 (Schriften des Hochschulverbandes, 13).

[40] See also *L. Meitner*, "The status of women in the professions", Phys. Today *13*, 17 (1960).

[41] See *e.g. B. L. van der Waerden*'s report about Leipzig in ref. [3], p. 116 sq., and 83; and *E. Berninger:* Otto Hahn in Selbstzeugnissen und Bilddokumenten. Rowohlt, Reinbek 1974 (rowohlts monographien, 204), p. 57 sq.

[42] Cf. *e.g. G. Schoenberner:* Der gelbe Stern. Die Judenverfolgung in Europa 1933—1945. C. Bertelsmann, Munich 1978; *H. D. Leuner:* Als Mitleid ein Verbrechen war. Limes, Wiesbaden 1967.

[43] Cf. *e.g. F. Herneck:* Albert Einstein, Ein Leben für Wahrheit, Menschlichkeit und Frieden. Buchverlag Der Morgen, Berlin ^{3}1967; *A. Hermann* in [1], p. 77 sqq.

[44] Archives of the Max Planck Society, Berlin.

[45] *A. Hermann* in [3], pp. 116—118.

[46] *O. Hahn* in [17], p. 91.

[47] *M. Born:* Mein Leben. Erinnerungen des Nobelpreisträgers. Nymphenburger Verlagshandlung, Munich 1975, p. 353 sq.

[48] See *L. Meitner* in [7c].

[49] *M. Planck*, "Mein Besuch bei Adolf Hitler". Physikalische Blätter *3*, 143 (1947).

[50] See ref. [46].

[51] See *O. Hahn*, "Zur Erinnerung an die Haber-Gedächtnisfeier vor 25 Jahren am 29. Januar 1935 im Harnack-Haus in Berlin-Dahlem", Mitt. Max-Planck-Ges. *1960* (Issue 1), 3; *E. Berninger* in [41], pp. 58—61.

[52] *O. Hahn* in [17], p. 92.

[53] See *e.g. M. von Laue*, "Zu Max Plancks 100. Geburtstag". Naturwissenschaften *45*, 221 (1958); (also in: Aufsätze und Vorträge. Vieweg, Braunschweig ^{2}1962, p. 257); *A. Hermann* in [1], p. 77; *M. Born* in [47], p. 354.

[54] *F. Glum* in [26], p. 378.

[55] *M. Born* in [47], p. 353 sq.

[56] Archives of the Max Planck Society, Berlin (literary estate of Otto Hahn), here quoted from *E. Berninger* in [41], p. 58.

[57] *L. Meitner*, "Wege und Irrwege zur Kernenergie", Naturwissenschaftliche Rundschau *16*, 167 (1963).—*Otto Hahn* always says "we" in that connection.

[58] Cf. *F. Krafft:* Ein Leben im Dienste der Chemie und des akademischen Nachwuchses. Professor Dr.-Ing. Fritz Strassmann zum fünfundsiebzigsten Geburtstag. Jahrbuch der Vereinigung "Freunde der Universität Mainz" 25/26 (1976/77), pp. 226—230. My monograph on the life and creative work of *Fritz Strassmann* ("Im Schatten der Sensation") is to be published shortly by Verlag Chemie, Weinheim. It will mainly consist of documents and personal records.

[59] *Irmgard Strassmann*, the second wife of *Fritz Strassmann*, remembers a remark which he made on that point at Berlin in 1935.

[60] In interviews with the author and in personal records from the seventies which he placed at my disposal.

[61] *O. Hahn, F. Strassmann*, "Über den Nachweis und das Verhalten der bei der Bestrahlung des Urans mittels Neutronen entstehenden Erdalkalimetalle", Naturwissenschaften *27*, 11 (1939).

[62] *W. Heisenberg* in [6], p. 113 sq.

[63] *W. Heisenberg* in [6], p. 116.

[64] Cf. the *Hahn-Meitner* correspondence (Nov. 1938—April 1939) edited (incompletely) by *D. Hahn* in *D. Hahn:* Otto Hahn, Erlebnisse und Erkenntnisse. Econ, Düsseldorf 1975, pp. 75—129.—Unfortunately the letters are rendered not very accurately and moreover there are omissions which are not marked. The omissions in letters of *Otto Hahn* include mainly detailed remarks on his official duties and problems regarding his family, which just could have shown that in the second half of 1938 he had hardly any time or patience for scientific work. Much more grave are omissions like the seemingly unimportant small sentence: "(*Strassmann* ist verreist.)", *i.e. Strassmann* is away, in *Otto Hahn*'s letter of December 28, 1938, that follows the sentences: "... and now comes my new phantasy. We have *not* proved that the transuranics are *not* Ma, Ru, Rh, Pd. At least I for my part know so little about those substances that I cannot exclude them chemically."

[65] *L. Meitner, O. R. Frisch*, "Disintegration of Uranium by Neutrons: A New Type of Nuclear Reaction", Nature *143*, 239 (1939) [No. 3615, February 11, 1939; submitted on Jan. 16, 1939). The joint publication was settled by telephone between Copenhagen *(Frisch)* and Stockholm.

[66] *W. Heisenberg* in [6], p. 116.

[67] See ref. [57]. After inquiries on the financial situation of the Emil Fischer Society, *Otto Hahn* filed on November 6, 1934, an application to the treasurer *Arthur von Weinberg* for the granting of 10—12000 RM "for the building of equipment for the splitting of nuclei by protons". Those means were transfered in two yearly instalments to a special account of the department of physics which was at *Lise Meitner*'s disposal (Max Planck Institute for Chemistry, Mainz, file 'Allgem. Angelegenheiten KWI für Chemie').—The apparatus on the so-called "workbench of *Otto Hahn*", exhibited at the Deutsches Museum at Munich—on the table there are also some instruments from the "Messzimmer" (measurements room) of *Lise Meitner*—had been arranged by *Lise Meitner* in 1934/35. It was used by her, *Otto Hahn*, and (in 1938 mainly) *Fritz Strassmann*.

[68] See ref. [61], p. 15.—*Fritz Strassmann* remembers that all the papers published jointly with him were written by *Otto Hahn* alone, and that he himself could not even look over them before they were completed.

[69] Cf. *O. Hahn:* a) Mein Leben. Bruckmann, Munich 1968, especially pp. 145—147; and above all b): Erinnerungen 1901—1945, in: *D. Hahn* [64], pp. 15—73 (especially pp. 50—56).

[70] *O. Hahn* in *D. Hahn* [64], p. 54 sq.

[71] Letter of *Lise Meitner* to *Otto Hahn* dated Feb. 23, 1947; Archives of the Max Planck Society, Berlin (literary estate of Otto Hahn).

[72] See especially her letter of June 24, 1947 to *Otto Hahn* (as in [71]).

[73] *L. Meitner* in [7a], p. 7.

[74] See ref. [70].

[75] *Georg Graue* was then assistant at the "National Socialist Model Institute" (*O. Hahn* in [69a], p. 149), the Kaiser Wilhelm Institute for Physical Chemistry and Electro-Chemistry at Berlin-Dahlem, the former institute of Haber.

[76] *Heinrich Hörlein* was treasurer of the "Emil Fischer Society for Advancement of Chemical Research", which sponsored the KWI for Chemistry.

[77] *Carl Bosch* (I.G. Farbenindustrie A.G.) had been president of the management committee of the KWI for Chemistry and in 1937 he succeeded *Max Planck* as president of the Kaiser Wilhelm Society.

[78] *Ernst Telschow* was managing director of the "Generalverwaltung" of the Kaiser Wilhelm Society and the later Max Planck Society.

[79] Quoted by *O. Hahn* in [69a], p. 149.—The (copy of the) letter has still not been found either in the archives of the Max Planck Society in Berlin or among the documents of the "Generalverwaltung" at Munich (information from *Rolf Neuhaus* and *Ursula Ringmann*, respectively).

[80] *O. R. Frisch* in [6a], p. 410. See also the report by *O. Hahn* in *D. Hahn* [64], p. 55.

[81] Facsimile of page 1 of the shorthand note in *E. Berninger:* Otto Hahn—Eine Bilddokumentation. Persönlichkeit—Wissenschaftliche Leistung—öffentliches Wirken. Moos, Munich 1969, p. 42, and in [41], 67.—The letter has not yet been found; see ref. [79].

[82] *Carl Bosch* was in poor health and had gone in vacation. Cf. *Otto Hahn*'s letter to *Lise Meitner* of October 1, 1938 (Archives of Churchill College, Cambridge, Meitner papers): "Having tried in vain, again and again, to ring up at the Adlon [a hotel at Berlin, where *Carl Bosch* used to live], I contacted the Geheimrat *[i.e. Carl Bosch]* the day before yesterday and yesterday I spent the afternoon with him. At first just the two of us, then with Dr. *Leist* [*Lise Meitner*'s

legal advisor at Berlin]. He confirmed what Dr. *T[elschow]* had already said. The Kaiser Wilhelm Society will try everything it can do for you and *Otto [Heidelberg]*. However, he doesn't know whether the applications [for exit permits] will be passed. As for you, perhaps a certain difficulty could have arisen in so far as in your case a personal consultation with "highest heaven" had been considered [in German: "mit dem obersten Himmel", *i.e.* with *Heinrich Himmler* (?)]. If they should find out now that you are not in Germany they would perhaps be cross ..." Cf. *Otto Hahn*'s letter to *Lise Meitner* of September 12, 1938 (*ibidem*): "... *Telschow* asked me today how the ministry knew about your departure—the ministry had asked him about it. I told him that in my opinion *Erb[acher]* and *Philipp* had told *Graue* about it and he had informed *M[entzel]*. Unfortunately it is still uncertain when *Bosch* will be back ..." Immediately after the institute vacation, on August 29, *Otto Hahn* had reported *Lise Meitner*'s decision to *Erbacher* and *Philipp* and thereafter to the whole staff (see the letter to *Lise Meitner* of that date, *ibidem*).

[83] *O. Hahn* in [17], p. 55, and in [69a], p. 149 sq.—The date of *Dirk Coster*'s arrival and *Lise Meitner*'s departure quoted by *Otto Hahn* (July 16/17, 1938) is certainly wrong, because he had already confirmed that he had heard about her successful flight in a postcard of July 15 (see ref. [84]).

[84] Postcard of *O. Hahn* to the *Coster* family of the July 15, 1938 (Archives of Churchill College, Cambridge, Meitner papers).

[85] See *Th. Nipperdey, L. Schmugge:* 50 Jahre Forschungsförderung in Deutschland. Ein Abriss der Geschichte der Deutschen Forschungsgemeinschaft 1920—1970. DFG, Bad Godesberg 1970, especially pp. 60—67; Ein Ehrentag der deutschen Wissenschaft: Die Eröffnung des Reichsforschungsrates am 25. Mai 1937. Hrsg. von der Pressestelle des Reichserziehungsministeriums. (Berlin 1937), especially p. 32.

[86] Transcript at Max Planck Institute for Chemistry (Otto-Hahn-Institut), Mainz (Personnel file Meitner).

[87] Max Planck Institut for Chemistry (Otto-Hahn-Institut), Mainz (Personnel file Meitner).

[88] Letter of *Otto Hahn* to *Lise Meitner* of September 8, 1938 (Archives of Churchill College, Cambridge, Meitner papers).

[89] Archives of the Max Planck Society, Berlin (literary estate of Otto Hahn).—The two letters mentioned in the letter have not yet been found; see ref. [79].

[90] See *O. R. Frisch* in: Niels Bohr, His Life and Work. Wiley, New York 1966; *R. Moore:* Niels Bohr. Ein Mann und sein Werk verändern die Welt. List, Munich 1970, p. 181 sqq. English version published by A. A. Knopf, New York 1970; *L. Meitner* in [7a], p. 7.

[91] See the correspondence in *D. Hahn* [64], which is to be supplemented by several other letters.

[92] Archives of the Max Planck Society, Berlin (literary estate of Otto Hahn).

[93] Because of that short trip it is nearly always erroneously stated that *Lise Meitner* emigrated *via* Holland *and* Denmark to Sweden.

[94] *Otto Hahn* had had the counter made at his institute in Berlin. It had been ordered by *Sieghahn*, as *Hahn* himself had proposed.

[95] On September 1, 1939, World War II began with the invasion of Poland by German troops.

[96] Archives of the Max Planck Society, Berlin (literary estate of Otto Hahn).

[97] See ref. [67].

[98] Archives of the Max Planck Society, Berlin (literary estate of Otto Hahn), and copy in the Archives of Churchill College, Cambridge (Meitner papers).

[99] See ref. [98].

[100] Letter to *Otto Hahn* of October 15, 1953; see ref. [98].

[101] She—and her friends—were very disappointed, when the Nobel prize for Chemistry of 1944 was awarded to *Otto Hahn* alone "for his discovery of the fission of heavy nuclei"—and that he accepted it for himself alone. Intimate colleagues therefore tried in 1946, when the decision of the prize of 1944 (set aside for *Otto Hahn*) was approaching, to suggest *Lise Meitner* as the co-winner. But on Nov. 15, 1946, she informed *Otto Hahn* in a postcard: "... The chance of becoming your Nob[el] Colleague is definitively finished. If you are interested, I can tell you something about that ..." (Archives of the Max Planck Society, Berlin, literary estate of Otto Hahn).

[102] Quoted in a letter of *Marie-Luise Rehder, Otto Hahn*'s secretary and co-worker of long standing, to *Irmgard Strassmann* of the August 10, 1966 (private archives of F. Strassmann).

[103] Cf. the letter of *Otto Hahn* to the Chairman of the General Advisory Committee *Manson Benedict* of Jan. 9, 1964 (copy in archives of F. Strassmann) replying to his repeated invitation of Jan. 6, 1964 to nominate a candidate for the prize: "... For a selection I should like to nominate my colleague Dr. *Fritz Strassmann*, sharing with me the result of the discovery of the fission of Uranium. As you may perhaps know, we have worked together for many years. Dr. *Strassmann* having been acquainted with the subject just as well as myself. As I have received the Nobel Price for the year of 1944 for the discovery of Uranium fission, I should think it justified if Dr. Strassmann would also receive a recognition of his very good and successful researches ..."

COMMUNICATIONS

Communications are brief preliminary reports of research work in all areas of chemistry which, on account of its fundamental significance, novelty, or general applicability, should be of interest to a broad spectrum of chemists. Authors of communications are requested to state reasons of this kind justifying publication on submission of their manuscript. The same reasons should be clearly apparent from the manuscript. In cases where the editorial staff decide, after due consultation with independent referees, that these conditions are not met, manuscripts will be returned to the authors with the request to submit them for publication in a specialist journal catering for scientists working in the field concerned.

Unusual Selectivity in the Thermal Rearrangement-Elimination Reaction of a Carbene Complex in Solution and in the Solid State [1]

By *Helmut Fischer, Andreas Motsch,* and *Willi Kleine*[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

Halocarbene complexes represent potential intermediates in the synthesis of carbyne complexes. The study of their reactivity should increase our understanding of the course of this reaction.

We have now found that pentacarbonyl[chloro(diethylamino)carbene]chromium[2] *(1a)* is transformed almost quan-

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titatively with loss of CO into *trans*-chlorotetracarbonyl(diethylaminocarbyne)chromium *(2a)* on warming to above 30 °C *in solution* in higher-boiling aliphatic and olefinic halocarbons, aromatic compounds, or ethers.

$$(CO)_5Cr{=}C\begin{matrix}X\\ \diagdown\\ \diagup\\ N(C_2H_5)_2\end{matrix} \xrightarrow{\Delta} X(CO)_4Cr{\equiv}CN(C_2H_5)_2 + CO \quad (A)$$

(1) *(2)*

(a): X = Cl
(b): X = Br

In contrast, warming of *solid (1a)* to above 30 °C leads to evolution of gas and to a brown coloration of the substance which affords chromium chlorides and undefined polymers, as well as pentacarbonyl(ethyl isocyanide)chromium *(3)* (26–29% yield, according to spectroscopy) as solid products; no *(2)* is formed. The seemingly likely conclusion that *(1a)* reacts *via* elimination of ethyl chloride is not correct; the only gaseous product apart from CO is hexacarbonylchromium and not ethyl chloride (b.p. 12.3 °C):

$$(1a) \xrightarrow[\text{solid}]{>30\,^\circ C} (CO)_5Cr(CNC_2H_5) + (CO)_6Cr + CO + \cdots \quad (B)$$

(3)

Pentacarbonyl[bromo(diethylamino)carbene]chromium[3] *(1b)* reacts *both in solution* (CH_2Cl_2) *and in the solid state* at temperatures above −20 °C according to eq. (A) *via* CO elimination to give the *trans*-bromocarbyne complex *(2b)*.

On the other hand, pentacarbonyl[(diethylamino)fluorocarbene]chromium[4] is thermally very stable and only decomposes above 100 °C. Neither formation of a *trans*-fluorocarbyne complex analogous to *(2)* nor that of another carbonylmetal derivative could be detected.

In order to gain information about the mechanism of the carbene—carbyne rearrangement (A) and possibly also about the course of reaction (B), we have performed a kinetic study on reaction (A). The reaction rates were determined by means of IR data [ν_{CO} of *(1a)*, 2063 m, 1939 vs cm^{-1}; ν_{CO} of *(2a)*, 2100 w, 2020 s, 1995 vs cm^{-1}; in 1,1,2-trichloroethane] in the case of *(1a)* and photometric data [increase in absorption shoulder at 490 nm] in the case of *(1b)*. The rate constants of the rearrangement-elimination reaction of *(1a)* and *(1b)*[5] are listed in Table 1; they show that reaction (A) follows 1st order kinetics:

$$-d[(1)]/dt = k[(1)]$$

Table 1. Rate constants k of reaction of *(1)* according to eq. (A). $[(1a)] = 0.01$ mol/l.

Complex	Solvent	T [°C]	$k \times 10^3$ [s^{-1}]
(1a)	1,1,2-Trichloroethane	31.5	0.59
		39.9	1.92
		47.5	4.61
		55.5	11.0
	1,1,2-Trichloroethane + CO [a]	47.5	4.53
	1,2-Dichloroethane	39.9	1.47
	1,1,2,2-Tetrachloroethane	39.9	5.74
	Trichloroethene	39.9	0.32
	Di-*n*-butyl ether	39.9	0.27
	Diglyme/HMPT (9:1) [b]	49.5	1.42
	Diglyme/HMPT (9:1) [b] + KCl (sat.)	49.4	1.41
(1b)	Dichloromethane	−30.6	0.59
		−23.8	1.30
		−19.2	2.70
		−16.1	4.41

[a] Solvent saturated with CO; CO as protective gas.
[b] HMPT = hexamethylphosphoric triamide.

The values of k depend upon the nature of the solvent; however, there does not appear to be any clear correlation between $\log k$ and $1/D$ or $[(D-1)/(2D+1)]$ (D = dielectric constant). As seen in Table 1, the rate of (A) is not influenced by free CO or by Cl^- in the solution. Even under 50 atm of CO, no significant drop in the reaction rate is observed. Determination of the activation parameters afforded:

(1a): $\Delta H^{\neq} = 23.7 \pm 0.5$ kcal/mol;
$\Delta S^{\neq} = 4 \pm 1$ cal/mol·K (in Cl_2CHCH_2Cl)

(1b): $\Delta H^{\neq} = 18 \pm 1$ kcal/mol;
$\Delta S^{\neq} = -1 \pm 2$ cal/mol·K (in CH_2Cl_2)

The following alternatives merit discussion as possible mechanisms:

a) Liberation of a CO ligand in the first and slowest reaction step (pentacoordinate transition state) and migration of the halogen from the carbene carbon atom to the *trans* position of the metal.

b) Homolytic or heterolytic cleavage of the halogen-carbon bond (hexacoordinate transition state) followed by CO elimination and readdition of the halogen in the *trans* position.

c) Migration of the halogen from the carbene carbon to the metal (heptacoordinate transition state) and loss of CO to form *(2)*.

Alternative (a) can be ruled out on the basis of the activation parameters and the negligible effect of free CO on the reaction rate. The very pronounced decrease in activation energy on going from *(1a)* to *(1b)* suggests rupture or at least pronounced weakening of the C—X bond in the first reaction step.—Evidence opposing formation of the cation $[(CO)_5CrCN(C_2H_5)_2]^+$ in the transition state comes from the lack of any dependence of the reaction rate upon the concentration of Cl^- and the observation that *(1a)* is formed instantaneously from $[(CO)_5CrCN(C_2H_5)_2]^+BF_4^-$ and Cl^- under the reaction conditions; only then does *(1a)* react further to give *(2a)*.—A decision between the two remaining possibilities of the intramolecular (route (c)) and free-radical mechanism (homolysis of the C—X bond) still remains open.

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[2] *E. O. Fischer, W. Kleine, F. R. Kreissl*, J. Organomet. Chem. *107*, C 23 (1976).
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[4] *E. O. Fischer, W. Kleine, F. R. Kreissl*, Angew. Chem. *88*, 646 (1976); Angew. Chem. Int. Ed. Engl. *15*, 616 (1976).
[5] *A. Motsch*, Diplomarbeit, Technische Universität München 1976.

$C_6H_5Sb[Mn(CO)_2C_5H_5]_2$—The First Compound Containing Trigonal-Planar Coordinated Antimony(I)[**]

By *Joachim von Seyerl* and *Gottfried Huttner*[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

Phosphinidene and arsinidene complexes containing phenylphosphanediyl[1] and phenylarsanediyl[2] as bridge ligands with trigonal-planar P^I and As^I, respectively, have already

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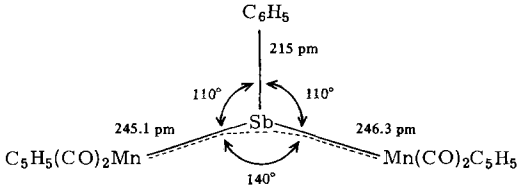
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

been reported. We have now also succeeded in stabilizing phenylstibanediyl, C_6H_5Sb, in a similar way.

The deep-red diiodo(phenyl)stibane complex *(1)* reacts with potassium in tetrahydrofuran (THF) if the reaction is catalyzed by [18]crown-6. In the presence of $C_5H_5(CO)_2Mn\cdot THF$, a product mixture is obtained from which the stibinidene complex *(2)* can be isolated in pure form by chromatography.

$$\underset{(1)}{C_5H_5(CO)_2MnSb(C_6H_5)I_2} + C_5H_5(CO)_2Mn\cdot THF \xrightarrow{K,\ [18]Crown\text{-}6,\ THF} \underset{(2)}{C_6H_5Sb[Mn(CO)_2C_5H_5]_2} + 2KI + \cdots$$

Compound *(2)* forms shiny golden metallic triclinic crystals, which after some initial decomposition at the crystal surface are stable in air. Their extremely air-sensitive solutions in toluene, dichloromethane or *n*-pentane are intense blue in color. In a closed tube, *(2)* melts at 127—128 °C. The mass spectrum corresponds to that of the P and As homologues: The molecular ion (m/e = 550 ref. to ^{121}Sb) is transformed by stepwise cleavage of two pairs of CO groups into the basic ion $C_6H_5Sb[MnC_5H_5]_2^+$ (m/e = 438); a further characteristic fragment is $C_6H_5SbMnC_5H_5^+$ (m/e = 318).—The IR spectrum of *(2)* shows a complex pattern of absorption bands [1966 (m), 1939 (s), 1907 (s), 1900 (m), 1829 (w) cm^{-1}], indicating the presence of rotamers.



The trigonal-planar coordination of the antimony was confirmed by an X-ray structure analysis[3]. The bond angles and bond lengths clearly indicate that the bridging group is stabilized by transition metal-antimony π-bonds.

The method used for the synthesis of *(2)* is also suitable for the preparation of arsinidene complexes.

Experimental

All operations must be carried out under N_2 in anhydrous solvents [Irradiation: Hanau TQ 150, Duran apparatus; structure: Syntex P3]. A solution of $C_5H_5(CO)_3Mn$ (1 g, 4.9 mmol) in THF (400 ml) is irradiated for 150 min. To the resulting red solution of $C_5H_5(CO)_2Mn\cdot THF$ is added bulkwise 2 g (3.2 mmol) *(1)*. A suspension of 480 mg (12 mmol) potassium and 200 mg (0.8 mmol) [18]crown-6 in 20 ml THF is stirred at −90 °C until development of an intense blue color. The two solutions are combined at −90 °C and allowed to warm within 1 h to room temperature. After removal of the solvent, the red residue is taken up in 30 ml toluene and filtered over silica gel at 20 °C, whereupon the color of the solution turns blue-green. The residue obtained after further removal of solvent is absorbed on 3 g silica gel from toluene and chromatographed at −30 °C (Silicagel Merck, particle size 0.063—0.2 mm, column 2.5 × 30 cm). The yellow front is removed from the column with *n*-pentane/CH_2Cl_2 (3:1); on further elution with *n*-pentane/CH_2Cl_2 (1:1) there follows a broad blue zone of *(2)*, which after chromatography and recrystallization from *n*-pentane/CH_2Cl_2 (1:1) affords 250 mg (15 %) of analytically pure *(2)*.

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(1), 68185-49-9; *(2)*, 68185-50-2; $C_5H_5(CO)_3Mn$, 12079-65-1

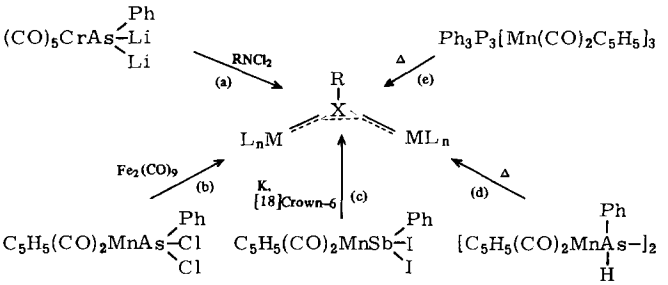
[1] *G. Huttner, H.-D. Müller, A. Frank, H. Lorenz*, Angew. Chem. *87*, 714 (1975); Angew. Chem. Int. Ed. Engl. *14*, 705 (1975).
[2] *G. Huttner, H.-G. Schmid*, Angew. Chem. *87*, 454 (1975); Angew. Chem. Int. Ed. Engl. *14*, 433 (1975); *G. Huttner, J. v. Seyerl, M. Marsili, H.-G. Schmid, ibid. 87*, 455 (1975) bzw. *14*, 434 (1975).
[3] Space group $P\bar{1}$, $Z=2$; $a=793.4$, $b=971.1$, $c=1337.3$ pm, $\alpha=108.7$, $\beta=92.5$, $\gamma=81.8°$; 1340 independent reflections; present $R_1=0.13$.

Facile New Synthesis of Chloroarsinidene Complexes[**]

By *Joachim von Seyerl, Ute Moering, Adalbert Wagner, Albin Frank*, and *Gottfried Huttner*[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

The methods (a)[1], (b)[2], (c)[3], (d)[4], and (e)[5] depicted in the following Scheme have previously been developed for the synthesis of phosphinidene, arsinidene and stibinidene complexes.



All these synthetic routes involve several steps and are laborious owing to the complicated working-up procedures; moreover, they enable preparation only of complexes in which R is an organic moiety.

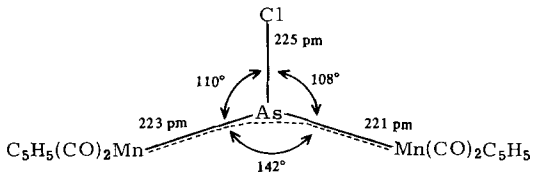
We have now found that arsinidene complexes with R = Cl are accessible in a surprisingly simple way: Reaction of $C_5H_5(CO)_2Mn\cdot THF$ with $AsCl_3$ in tetrahydrofuran (THF) leads to an intense violet solution, from which the chloroarsinidine complex $ClAs[Mn(CO)_2C_5H_5]_2$ *(1)* can be isolated chromatographically in the form of shiny black crystals, m. p. 123—124 °C.

The IR spectrum of *(1)* (*n*-pentane) shows the characteristic pattern of absorption bands for $RX[Mn(CO)_2C_5H_5]_2$ (X = P[5], As[1], Sb[3]), which, with four bands at 2002 (m), 1963 (s), 1950 (m), 1920 (m) cm^{-1}, indicates the presence of a rotameric equilibrium.—The ^1H-NMR signal (C_6D_6) of the cyclopentadienyl protons appears at δ = 4.25 rel. to TMS ext. The mass spectrum shows, besides the molecular ion (m/e = 462 ref. to ^{35}Cl), two series of fragments introduced by initial cleavage of the Cl atom or the CO groups; the base peak corresponds to $As(MnC_5H_5)_2^+$ (m/e = 315).

The expected trigonal-planar coordination of the arsenic in *(1)* is confirmed by the X-ray structure analysis[6].

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Also observed is the shortening of the Mn—As distances consistent with the assumed bonding scheme[7], which in the case of *(1)* are shorter again than in the analogous phenylarsinidene complex (227 pm[4]) owing to the electronegative chlorine substituent. The functional groups on the arsenic atom make *(1)* an interesting starting compound for many other reactions. That the present unsatisfactory yields can be considerably improved is indicated, for example, by the analogous synthesis of $ClAs[Cr(CO)_5]_2$ (present yield 20 %).

Experimental

All operations must be carried out under N_2 in anhydrous solvents [irradiation: Hanau TQ 150, Duran apparatus; structure: Syntex P3]. A solution of $C_5H_5(CO)_3Mn$ (5 g, 24 mmol) in THF (400 ml) is irradiated for 2 h. The resulting solution of $C_5H_5(CO)_2Mn \cdot THF$ is stirred together with 2 ml (4.32 g, 24 mmol) $AsCl_3$ for 10 h at 20 °C. After removal of solvent at 20 °C the residue is taken up in 20 ml of toluene and filtered through a 3-cm layer of silica gel. The violet reaction product recovered from this solution on 3 g silica gel is chromatographed at −30 °C (silica gel Merck, particle size 0.063—0.200 mm, column 2.5 × 30 cm). $C_5H_5(CO)_3Mn$ is washed from the column with *n*-pentane; subsequent elution with *n*-pentane/CH_2Cl_2 (1 : 1) affords a broad red-violet zone of *(1)*, from which black crystals of analytically pure *(1)* can be obtained in 6.6 % yield (500 mg) by recrystallization from *n*-pentane/CH_2Cl_2 (1 : 1).

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CAS Registry numbers:
(1), 68185-28-4; $C_5H_5(CO)_3Mn$, 12079-65-1; $AsCl_3$, 7784-34-1

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[6] Space group $P2_1/c$, $Z=4$; $a=899.2$, $b=1513.8$, $c=1178.9$ pm, $\beta=80.02°$; 1112 independent reflections ($I \geq 3\sigma$), $R_1=0.053$.
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A Substitution with Retention at the Cyclopropane Ring[**]

By *Jürgen Schäffler* and *János Rétey*[*]

Cobalt-substituted cyclopropanes could be of importance in coenzyme B_{12}-catalyzed rearrangements[1]. We have been unable to find any reference to this class of compounds in the literature, apart from in one short communication[2]. In order to attempt a direct substitution at a cyclopropane ring by cobalt(I), we prepared the "*endo*" and "*exo*" isomers *(1)* and *(2)* of doubly benzoannelated 7-bromonorcarane, which itself was obtained by reduction of the 7,7-dibromo derivative *(3)*[3] with tri-*n*-butyltin hydride and subsequent chromatographic purification. The NMR signals of the protons geminal to bromine (see Table 1) permitted unequivocal assignment of the *endo* and *exo* configurations to *(1)* and *(2)*, respectively.

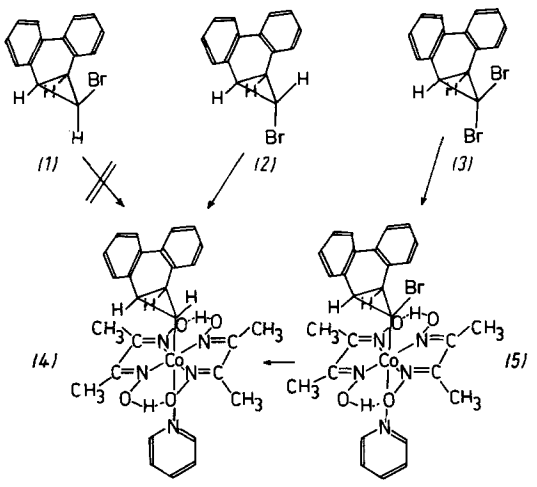


Table 1. Physical data of compounds *(1)*—*(5)*. *(1)*—*(4)* gave correct analytical data.

(1): M.p. = 104—105 °C; ^{1}H-NMR ($CDCl_3$): $\delta=2.95$ (d, $J=8$ Hz, 2H), 3.71 (q, $J=8$ Hz, 1H), 7.3—7.5 (m, 6H), 7.9—8.2 (m, 2H); MS (*m/e*) *inter alia* 191 (100 %), 192 (26.5), M^+ 270/272 (1/1)
(2): M.p. = 111—112 °C; ^{1}H-NMR ($CDCl_3$): $\delta=2.32$ (t, $J=3$ Hz, 1H), 2.90 (d, $J=3$ Hz, 2H), 7.3—7.6 (m, 6H), 7.95—8.05 (m, 2H); MS (*m/e*) *inter alia* 191 (100 %), 192 (17), M^+ 270/272 (4/4)
(3): M.p. = 125—126 °C; ^{1}H-NMR (CCl_4): $\delta=3.42$ (s, 2H), 7.2—7.6 (m, 6H), 7.85—8.05 (m, 2H); MS (*m/e*) *inter alia* 269 (100 %), 270 (19.5), 271 (98), 272 (17.5), M^+ 348/350/352 (2.5/5/2.5)
(4): UV/VIS, $\lambda_{max}=457$ nm; ^{1}H-NMR ($CDCl_3$): $\delta=0.7$ (t, $J=4.5$ Hz, 1H), 1.67 (d, $J=4.5$ Hz, 2H), 2.2 (s, 12H), 7.0—7.4 (m), 7.65—7.9 (m), 8.6 (m)
(5): UV/VIS, $\lambda_{max}=458$ nm; ^{1}H-NMR ($CDCl_3$): $\delta=2.25$ (s, 12H), 2.38 (s, 2H), 7.0—7.4 (m), 7.65—7.9 (m), 8.6 (m)

Reaction of *(2)* with cobal(I)oxime[4] gave the cobaloxime derivative *(4)* (see *Experimental*). Both the spectroscopic data of the product (Table 1) and model considerations are reconcilable only with the *exo* structure *(4)*; the *endo* cobaloxime would be sterically unrealizable owing to the dihydrophenanthrene "protective shield".

In contrast to *(2)* the *endo* isomer *(1)* cannot be substituted by cobal(I)oxime, even on prolonged reaction. Cobaloxime *(4)* is also obtained, along with the bromine-containing cobaloxime *(5)*, from the dibromo derivative *(3)*.

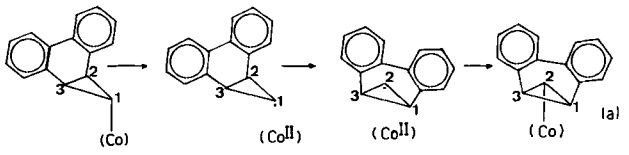
The orange-yellow crystalline product *(4)* showed a temperature-dependent ^{1}H-NMR spectrum in perdeuterated hexamethylphosphoric triamide. The signals of the cyclopropane protons at $\delta=0.60$ and 1.70 are broadened at 120 °C, but between 160 and 190 °C they are once again observable as a sharp triplet ($\delta=0.35$) and doublet ($\delta=1.55$). This behavior can be explained in terms of a rapid exchange of the pyridine ligand with solvent molecules. The assumed degenerate rearrangement according to Eq. (a) could not be observed up to 190 °C.

Several mechanisms for the substitution by cobalt(I) have been discussed[2, 5, 6]. A classical S_N2 substitution of the cyclo-

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propane derivatives *(1)* and *(2)* is considered unlikely[7]. The smooth substitution of the *exo*-isomer *(2)* supports the conclusion of *Breslow* and *Khanna*[6] that cobalt(I) complexes can also react with alkyl halides with one-electron transfer:



after elimination of the halide ion the Co—C bond can be formed by combination of the cobalt(II) complex and the alkyl radical. A similar type of substitution cannot take place in the *endo* bromide *(1)* owing to steric hindrance. The retention of configuration observed during the transformation of *(2)* into *(4)* is most likely due to shielding by the dihydrophenanthrene moiety. A retentive alkylation of cobalt(I) oxime has recently also been observed with other sterically hindered alkyl halides[8].

Experimental

A solution of $CoCl_2 \cdot 6H_2O$ (238.6 mg, 1 mmol) and 2,3-butanedione dioxime (232.5 mg, 2 mmol) in analytically pure methanol (60 ml) is prepared under argon. On addition of 2 ml 1 M KOH and 1 ml 1 M pyridine (both in methanol), a color-change from pink to brownish orange is observed. The solution is cooled to -10 °C and treated with a suspension of 80—400 mg (2—10 mmol) $NaBH_4$ (recrystallized from diglyme[9]) in 1 ml 1 M methanolic KOH. After stirring for one hour, the solution turns black; it is now treated dropwise with a solution of 1 mmol *(1)*, *(2)*, or *(3)* (experiments a, b, c) in 30 ml methanol or THF. After 12 h (up to 3 d in the case of a) at room temperature the methanol is removed *in vacuo* and the residue chromatographed on 20 g silica gel (Merck, 0.05—0.2 mm) with ethyl acetate. Yields: a) 90% unchanged *(1)*; b) 7% *(4)* and 27% dibenzoannelated norcarane[10]; c) 60% unchanged *(3)*, 27.5% *(1)*, 4.5% *(2)*, 4—10% *(4)*, and 1—4% (depending on reaction time and amount of $NaBH_4$ used) *(5)*.

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(1), 68129-59-9; *(2)*, 68170-56-9; *(3)*, 68129-60-2; *(4)*, 68129-67-9; *(5)*, 68129-66-8

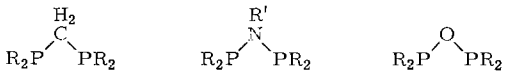
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Stabilization of a Phosphinic Anhydride R_2POPR_2 on Gold(I) and Formation of the Trinuclear Complex $(R_2POAu)_3$—Production of an Octahedral Structural Unit $Ag_4Br_2^{2+}$ by Clamping with $R_2PN(R')PR_2$

By *Hubert Schmidbaur, Aref A. M. Aly*, and *Ulrich Schubert*[*]

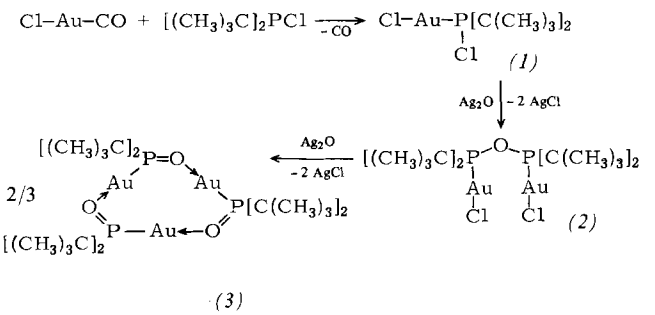
Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

Phosphinic anhydrides (diphosphoxanes) $R_2P—O—PR_2$ are generally unstable and isomerize to $R_2P—P(O)R_2$[1a]. Thus the hydrolysis of halodiorganophosphanes leads not to the acids R_2POH, but to their isomers $R_2P(O)H$ with a P—H bond[1b]. Compounds of type R_2POPR_2 are of considerable potential interest as ligands, since complexes of the analogous imino- and methylene-bisphosphanes exhibit unusual coordination properties[2, 3].



We have prepared the gold complex *(1)*, m.p. 135 °C (dec.), in quantitative yield from carbonylchlorogold(I) and di-*tert*-butylchlorophosphane *via* elimination of CO. The product is characterized by ν(AuCl) and ν(PCl) bands at 344 and 335 (^{35}Cl, ^{37}Cl) and 370 and 566 cm^{-1}, respectively. Its NMR spectra confirm the strong coordination of the chlorophosphane to the gold atom [$^{31}P\{^1H\}$: $\delta P = 144.1$, s; $^{13}C\{^1H\}$: $\delta PC = 40.51$, d, $^1J(PC) = 14.65$ Hz, $\delta PCC = 27.30$, d, $^2J(PC) = 7.32$ Hz; ^1H: $\delta CH_3 = 0.38$, d, $^3J(PH) = 18$ Hz; all spectra in C_6D_6].

Reaction of *(1)* with a substoichiometric amount of silver oxide in benzene over a period of 2 weeks at 20 °C affords AgCl and the benzene-soluble product *(2)*, which crystallizes on addition of pentane (yield 60%). Cryoscopic molecular mass determination in acetone confirms the formula given for the colorless compound, m.p. 287 °C (dec.). In the IR spectrum a strong broad signal appears at 895 cm^{-1} which is assigned to ν(POP)[4], while ν(PCl) is absent; ν(AuCl) remains almost constant at 345 and 335 cm^{-1}. The four *tert*-butyl groups are chemically equivalent (^1H-NMR: $\delta CH_3 = 1.70$, d, $^3J(PH) = 16.0$ Hz). The structure proposed on the basis of these data fits into the series of gold complexes of bisphosphanes, whose structures have also been elucidated by X-ray methods in some cases[3c, d].



Surprisingly, further reaction of *(2)* with Ag_2O or of *(1)* with an excess of Ag_2O does not lead to a diphosphoxane complex of gold(I) oxide Au_2O, but instead to a 75% yield of a colorless and benzene-soluble product of m.p. 301 °C

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(dec.): this product was identified as a novel trinuclear gold(I) di-*tert*-butylphosphinite *(3)*. Apart from complete elemental analysis, the mass spectrum is particularly informative; it shows the molecular ion of the trimer ($m/e = 1074$, $3 \times {}^{197}Au$) and fragments formed by loss of butyl groups and entire phosphinite units ($m/e = 1016$, 961, 903, 857, 799, 463, 405, 358, 303). In the IR spectrum of *(3)* there are no bands due to ν(AuCl) or ν(POP), and a new band appears at 995 cm^{-1} ν(P=O...Au). The six *tert*-butyl groups give just one doublet in the ^{1}H-NMR spectrum [$\delta CH_3 = 0.60$, $^3J(PH) = 15.0$ Hz], thus revealing the symmetry of the trimeric structure. Such a structure is still unknown for metal phosphinites[1b]; the formally analogous compound $(C_6H_5)_2POAg$ has been described as an insoluble coordination polymer[5]. In a classical study on the hydrolysis of halophosphane-platinum complexes, the present structural phenomena were anticipated for the neighboring element[6].

We obtained a silver complex of 1,1,3,3-tetraphenyl-2-methyldiphosphazane on reaction of the ligand with AgBr in CH_2Cl_2. The sparingly soluble crystalline product, m. p. 273 °C (dec.), was found analytically to be a 1:2 complex. X-Ray structure analysis[7] revealed the presence of dimeric molecules $\{CH_3N[P(C_6H_5)_2AgBr]_2\}_2$ containing a Ag_4Br_2 octahedron as central unit (Fig. 1). The basal plane made up of four silver atoms is bridged along two sides by two bromine atoms, and the apices of the polyhedron are occupied by two tetragonal-pyramidally coordinated bromine atoms. The other two edges of the base are spanned by PNP units in such a way that slightly twisted chair- and boat-like six-membered rings $BrAg_2P_2N$ can arise.

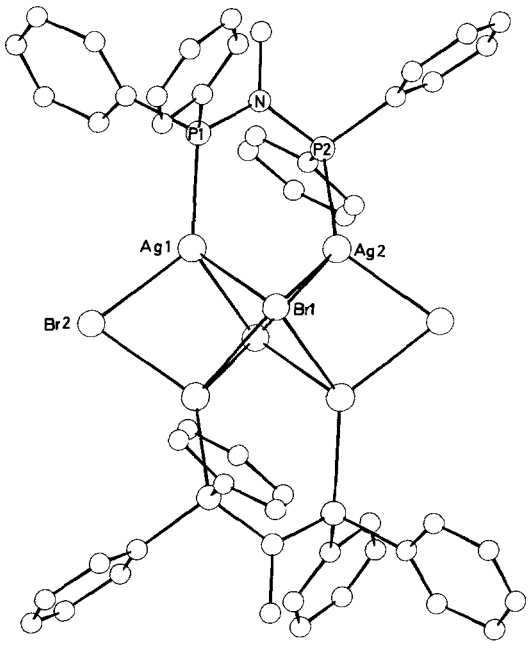


Fig. 1. Structure of the compound $\{CH_3N[P(C_6H_5)_2AgBr]_2\}_2$. The molecule is centrosymmtric.

Selected distances [pm] and angles [°].

Ag1—Ag2	296.4 (3)	Ag1—Br1—Ag2	60.0 (1)
Ag1—Ag2′	308.1 (2)	Ag1—Br1—Ag1′	95.2 (1)
Ag1—Br1	297.2 (4)	Ag1—Br1—Ag2′	64.0 (1)
Ag1—Br1′	276.3 (4)	Ag2—Br1—Ag2′	96.2 (1)
Ag2—Br1	296.0 (5)	Ag1—Br2—Ag2	73.2 (1)
Ag2—Br1′	283.6 (3)	Br—Ag1—Br	84.8 (1)—96.1 (1)
Ag1—Br2	258.9 (5)	Br—Ag2—Br	83.8 (1)—99.7 (1)
Ag2′—Br2	257.9 (5)	Br—Ag1—P1	101.7 (2)—134.4 (2)
Ag1—P1	238.0 (5)	Br—Ag2—P2	113.1 (2)—130.4 (2)
Ag2—P2	239.1 (6)	Ag1—P1—N	117.5 (7)
P1—N	171 (2)	Ag2—P2—N	115.5 (6)
P2—N	168 (2)	P1—N—P2	119 (1)

Unlike *methylene*bisphosphane complexes, which contain Ag_3Br_2 polyhedra[2a], the *imino*bisphosphoranes prefer Ag_4Br_2 polyhedra with greater edge lengths in the same system. We suspect the reason to lie in the difference between the PCP and PNP bond angles[2, 3].

Procedure

A solution of $[(CH_3)_3C]_2PCl$ (0.37 g, 2.0 mmol) in benzene is slowly added to a benzene solution of ClAuCO (0.40 g, 1.5 mmol), whereupon evolution of CO immediately ensues. After 2 h at 20 °C, the solvent can be removed under vacuum; the residue is washed and recrystallized from benzene/pentane. Yield 0.62 g (100 %); colorless substance, soluble in acetone, benzene, CH_2Cl_2.—*(1)* (1.00 g, 2.4 mmol) is stirred at 20 °C for 14 d with Ag_2O (0.42 g, 1.8 mmol) in benzene; AgCl precipitates. Filtration, removal of solvent, and addition of pentane afford colorless, light-sensitive *(2)* (0.55 g, 60 %).

Reaction of *(2)* with Ag_2O (1.9 mmol) in benzene or of *(1)* with an excess of Ag_2O gives further AgCl, and colorless, light-sensitive *(3)* can be isolated analogously from the filtrate; it is soluble in ether, acetone, and CH_2Cl_2.

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[7] 2102 structure factors ($F_0 \geq 5\sigma(F_0)$, Syntex $P2_1/XTL$, $Mo_{K\alpha}$, $3° \leq 2\theta \leq 48°$); $R = 0.085$. Monoclinic, space group $P2_1/c$, $a = 11.360(7)$, $b = 16.033(12)$, $c = 16.891(12)$ pm, $\beta = 122.36(4)°$, $V = 2599 \times 10^6$ pm^3, $Z = 2$.

Pentacyclo[6.4.0.0^{2,5}.0^{3,10}.0^{4,9}]dodeca-6,11-diene, an *o,o′*:*o,p′*-Dimer of Benzene[**]

By *Hans-Dieter Martin* and *Peter Pföhler*[*]

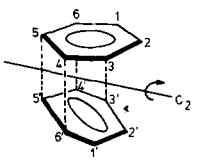
Dimers of benzene are of interest because aromatic resonance already becomes partly effective in the transition state of their thermal decomposition to benzene. Moreover, these $(CH)_{12}$ hydrocarbons are suitable for the study of intramolecular π,π- and π,σ-interactions owing to their compara-

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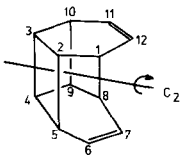
[**] Small Rings, Part 29. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Prof. Dr. *R. Gleiter* for recording the PE spectrum of *(2)*.—Part 28: *H.-D. Martin, B. Heiser, M. Kunze,* Angew. Chem. *90*, 735 (1978); Angew. Chem. Int. Ed. Engl. *17*, 696 (1978).

tively rigid skeletons. We now report the synthesis, thermolysis kinetics, and intramolecular interactions of the fourfold bridged benzene dimer *(2)*[1], which could be expected *a priori* to have a greater thermal stability than *o,o'*- and *o,p'*-dibenzenes[2].

The relationship between *(2)* and benzene is expressed schematically by *(1)*, which also underlines the C_2 symmetry present.

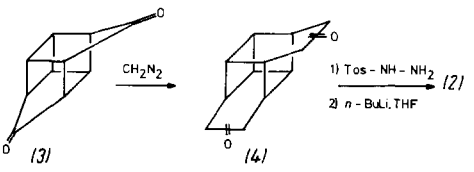


(1)



(2)

Treatment of bishomocubanedione *(3)* with diazomethane yields a mixture of the homologous diketones *(4)*[3]. Reaction with tosylhydrazine in tetrahydrofuran leads to the isomeric hydrazones. The action of *n*-butyllithium in THF on the mixture at room temperature affords a 22% yield of the diene *(2)*, which is purified by distillation and subsequent gas chromatography. Compound *(2)* is a colorless, slightly air-sensitive liquid having an uncharacteristic odor[4].



(3) *(4)*

The predominant fragmentation to benzene induced by electron impact is also observed on heating. After 2h at 190°C in hexachlorobutadiene, *(2)* has decomposed quantitatively to benzene. The kinetics of the unimolecular reaction was measured in mesitylene (Table 1).

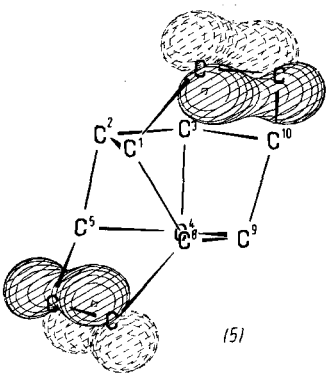
Table 1. Decomposition of *(2)* in mesitylene.

T[°C]	$10^5 \cdot k$ [s^{-1}]	E_a	log$A$
160.1	2.8	36.9 ± 0.3 kcal/mol 154.2 ± 1.3 kJ/mol	14.1 ± 0.2
166.7	5.4		
169.5	6.9		
172.2	8.9		
179.7	18.4		
185.3	29.2		

The activation energy of 36.9 kcal/mol is of the same order of magnitude as the values for basketene (29.7 kcal/mol)[5a] and homobasketene (35.3 kcal/mol)[5b]. The thermal reaction might involve a [4+2] cycloreversion to *o,o'*-dibenzene and its [2+2] fragmentation to benzene.

The formally nonconjugated double bonds in *(2)* could at first sight create the impression that there is no interaction between them. This is not the case. Although the topology of the molecule rules out direct π overlap (homoconjugation), considerable hyperconjugational effects can be expected. Possible transmitters are the 1,8-σ bond and the bicyclo[2.2.0]hexane moiety (C atoms 2,5,4,9,10,3), the latter case being without precedent. CNDO/S calculations[6] predict the energy sequence π_S (HOMO, $\varepsilon = -9.09$ eV) > π_A (third highest occupied MO, $\varepsilon = -9.76$ eV). The splitting of 0.7 eV is due to σ,π-interaction of π_S with σ(1,8) and with the bicyclo[2.2.0]hexane unit.

The perspectively correct structural formula *(5)*[7], which also contains the π-electron densities of the π_S HOMOs, reveals that both the 1,8-σ bond and the four-membered ring bonds



(5)

5,4 and 10,3 could engage in σ,π interaction. These model considerations are confirmed by experiment. The photoelectron spectrum of *(2)* gives $IP_{1,v} = 8.30$ eV and $IP_{2,v} = 9.35$ eV; the second band is more than three times as intense as the first one. Since basketene[8] shows $IP_{1,v} = 8.97$ eV and the inductive effect of an additional vinylene group on $IP_{1,v}$ can be neglected[9] [*(2)* can be regarded as vinylogous to basketene], a through-bond interaction of the kind mentioned above is held responsible for the lowering of $IP_{1,v}$ by $\Delta IP \approx 0.7$ eV.

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CAS Registry numbers:
(2), 68109-02-4; *(3)*, 14725-77-0

[1] The designation ansaradienes (*ansa*, Latin handle; *sari*, New Greek cube) is proposed for these bis-vinylogous cubanes. Thus *(2)* (point group C_2) is called C_2-ansaradiene and hence distinguished from the C_{2v} and D_{2h} isomers.

[2] *W. Grimme, E. Schneider*, Angew. Chem. *89*, 754 (1977); Angew. Chem. Int. Ed. Engl. *16*, 717 (1977), and references cited therein.

[3] *K. Hirao, E. Abe, O. Yonemitsu*, Tetrahedron Lett. *1975*, 4131.

[4] ^{1}H-NMR (CCl_4, 90 MHz): δ = 2.11 (mc; 4H; 1-H, 3-H, 4-H, 8-H), 2.53 (m; 2H; 2-H, 9-H), 3.40 (m; 2H; 5-H, 10-H), 5.94 ("t"; 2H; 6-H, 11-H), 6.34 ("t"; 2H; 7-H, 12-H).—MS (70 eV): *m/e* = 156 (1%, M^+), 78 (100%, $M - C_6H_6$).—IR: 1610 cm^{-1} (C=C).

[5] a) *H. H. Westberg, E. N. Cain, S. Masamune*, J. Am. Chem. Soc. *91*, 7512 (1969); b) *W. Mauer, W. Grimme*, Tetrahedron Lett. *1976*, 1835.

[6] *H. H. Jaffé*, Acc. Chem. Res. *2*, 136 (1969).

[7] *W. L. Jorgensen*, Quantum Chemistry Program Exchange *10*, 340 (1977).

[8] *R. J. Boyd, J.-C. G. Bünzli, J. P. Snyder*, J. Am. Chem. Soc. *98*, 2398 (1976).

[9] Cf. 1,3-cycloheptadiene → bicyclo[4.2.1]nonatriene: *P. Bischof, R. Gleiter, E. Heilbronner*, Helv. Chim. Acta *53*, 1425 (1970).

Existence of a New C_6H_6 Isomer: Tricyclo[3.1.0.0^{2,6}]hex-1(6)-ene[**]

By *Ursula Szeimies-Seebach, Joachim Harnisch, Günter Szeimies, Maurice Van Meerssche, Gabriel Germain*, and *Jean-Paul Declerq*[*]

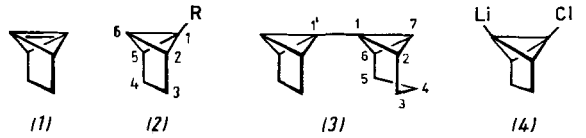
Cumulative evidence has become available for the formation of tricyclo[4.1.0.0^{2,7}]hept-1(7)-ene as a shortlived interme-

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diate[1]. We now report experimental results from which we deduce that the homologous title compound *(1)* can also exist as a reactive species. This new C_6H_6 isomer has the carbon skeleton of benzvalene, from which it differs in the position and energy of its CC double bond.



(2)	a	b	c	d	e
R	H	Li	Cl	n-C_4H_9	C_6H_5

Tricyclo[3.1.0.0^{2,6}]hexane *(2a)*[2] could be metalated with *n*-butyllithium in diethyl ether to give *(2b)*, which afforded a 48% yield of 1-chlorotricyclo[3.1.0.0^{2,6}]hexane *(2c)* on treatment with *p*-toluenesulfonyl chloride[3]. Compound *(2c)* reacts with organolithium compounds by nucleophilic substitution: *n*-butyllithium (molar ratio 1:3) gave an essentially quantitative yield of 1-*n*-butyltricyclo[3.1.0.0^{2,6}]hexane *(2d)* after aqueous workup, and phenyllithium the 1-phenyl derivative *(2e)* in 65% yield. The preparation of 1-(1-tricyclo[3.1.0.0^{2,6}]hexyl)tricyclo[4.1.0.0^{2,7}]heptane *(3)* was accomplished in 25% yield by combination of *(2c)* and 1-tricyclo[4.1.0.0^{2,7}]heptyllithium.

We interpret the course of these reactions as follows: the 1-chloro derivative *(2c)* is lithiated at C-6 by the lithium base to give *(4)*, which undergoes LiCl elimination to form the intermediate *(1)*. The bicyclo[1.1.0]but-1(3)-ene derivative *(1)* adds the lithium base to its highly strained double bond; aqueous workup then leads to the products [*(2d)*, *(2e)*, and *(3)*].

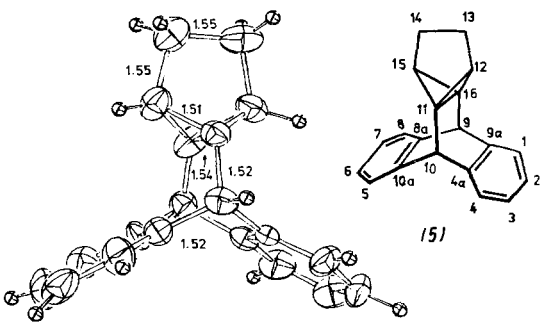
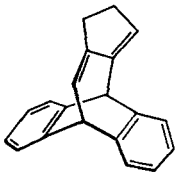


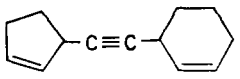
Fig. 1. Molecular structure of *(5)* with the principal bond lengths [Å]. The dihedral angle in the bicyclo[1.1.0]butane system is 113°. Bond angles: (C-12)—(C-11) (C-15), 91°; (C-10)—(C-11)—(C-16), 110°; (C-11)—(C-12)—(C-13), 109°; (C-12)—(C-13)—(C-14), 101°; (C-12)—(C-11)—(C-16), 59°.

Our interpretation of the reaction proceeding *via (1)* as intermediate is based on the formation of the Diels-Alder adduct *(5)*, which was isolated in 36% yield from a mixture of *(2c)*, lithium 2,2,6,6-tetramethylpiperidide, and anthracene in tetrahydrofuran at −20°C (m.p. 155–157°C, from *n*-pentane).

Structural proof for *(5)* is based on spectroscopic data (Table 1) and on an X-ray analysis depicted in detail in Figure 1[4]. The bridgehead atoms C-11 and C-16 of the bicyclo[1.1.0]-butane system of this [4.1.1]propellane[1c] exhibit the "inverted tetrahedron" phenomenon[5], *i.e.* C-11 and C-16 are each located outside the tetrahedron formed by their four respective substituents. Thus the distance between C-11 and the tetrahedral face C-10, C-12, C-15, which intersects the (C-11)—(C-16) bond, is 0.31 Å[6]. The (C-11)—(C-16) bond is significantly longer at 1.54 Å than the corresponding bonds in the other bicyclo[1.1.0]butanes examined so far[7].

At 150°C in C_6D_6, *(5)* undergoes complete rearrangement within 30 min to the diene *(6)* (cf. [1c]).—Compound *(3)* also isomerizes quantitatively at 160°C to the acetylene *(7)*.


(6)



(7)

Table 1 lists NMR data of the new compounds.

Table 1. NMR data (δ values) of *(2c)*, *(2d)*, *(2e)*, *(3)*, *(5)*, *(6)*, and *(7)*.

(2c): ^{1}H-NMR (C_6D_6): 0.91—1.53 (m; 4H, 3-H_2, 4-H_2), 2.10 (t, J = 2 Hz; 1H, 6-H), 2.22 (d, J = 2 Hz; 2H, 2-H, 5-H)

(2d): ^{1}H-NMR (CCl_4): 0.90 (t, J = 6 Hz; 3H, CH_3), 1.15—1.47 (m; 10H, $(CH_2)_3$, 3-H_2, 4-H_2 (last two proton groups as s at 1.23)), 1.53 (br. s; 1H, 6-H), 1.85 (narrow m; 2H, 2-H, 5-H)

(2e): ^{1}H-NMR (CCl_4): 1.40 (s; 4H, 3-H_2, 4-H_2), 2.02 (br. s; 1H, 6-H), 2.49 (d, J = 2 Hz; 2H, 2-H, 5-H).—^{13}C-NMR ($CDCl_3$): 16.94 (d; C-6), 20.40 (s; C-1), 25.84 (t; C-3, C-4), 37.12 (d; C-2, C-5); aromatic C: 124.59 (d), 126.11 (d), 127.89 (d), 137.70 (s)

(3): ^{1}H-NMR (CCl_4): 1.11 (t, J = 3 Hz; 1H, 7-H), 1.29 (broadened s; 10H, 3-H_2, 4-H_2, 5-H_2, 3′-H_2, 4′-H_2), 1.58 (br. s; 1H, 6′-H), 1.97 (d, J = 1.5 Hz; 2H, 2′-H, 5′-H), 2.28 (m; 2H, 2-H, 6-H).—^{13}C-NMR ($CDCl_3$): 7.41 (d; C-6′), 10.90 (d; C-7), 14.76 (s; C-1′), 16.29 (s; C-1), 20.48 (t; C-3, C-5), 21.01 (t; C-4), 26.15 (t; C-3′, C-4′), 37.83 (d; C-2′, C-5′), 43.78 (d; C-2, C-6)

(5): ^{1}H-NMR ($CDCl_3$): 1.37 (s; 4H, 13-H_2, 14-H_2), 2.00 (s; 2H, 12-H, 15-H), 4.65 (s; 2H, 9-H, 10-H), 6.90—7.47 (AA′BB′ system; 8H, aromatic H).—^{13}C-NMR ($CDCl_3$): 26.00 (s; C-11, C-16), 27.34 (t; C-13, C-14), 44.17 (d; C-9, C-10), 53.21 (d; C-12, C-15); aromatic C: 124.14 (d), 125.75 (d), 142.50 (s)

(6): ^{1}H-NMR (C_6D_6): 1.93 (s; 4H), 4.17 (d, J = 8 Hz; 1H), 4.70 (s; 1H), 5.70—6.07 (m; 2H), 6.83—7.42 (m; 8H)

(7): ^{13}C-NMR ($CDCl_3$): 20.81 (t), 24.77 (t), 27.61 (d), 29.83 (t), 31.97 (t), 32.04 (t), 36.02 (d), 82.50 (s), 83.08 (s), 126.94 (d), 127.99 (d), 130.84 (d), 132.04 (d)

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CAS Registry numbers:
(1), 68108-93-0; *(2a)*, 287-12-7; *(2b)*, 68108-94-1; *(2c)*, 68108-95-2; *(2d)*, 68108-96-3; *(2e)*, 68108-97-4; *(3)*, 68108-98-5; *(5)*, 68108-99-6; *(6)*, 68109-00-2; *(7)*, 68109-01-3; 1-tricyclo[4.1.0.0^{2,7}]heptyllithium, 66464-70-8

[1] a) *G. Szeimies, J. Harnisch, O. Baumgärtel*, J. Am. Chem. Soc. *99*, 5183 (1977); b) *G. Szeimies, J. Harnisch, K.-H. Stadler*, Tetrahedron Lett. *1978*, 243; c) *U. Szeimies-Seebach, G. Szeimies*, J. Am. Chem. Soc. *100*, 3966 (1978); d) *J. Harnisch, H. Legner, U. Szeimies-Seebach, G. Szeimies*, Tetrahedron Lett. *1978*, 3683.

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[3] *G. Szeimies, F. Philipp, O. Baumgärtel, J. Harnisch*, Tetrahedron Lett. *1977*, 2135.

[4] *(5)* forms monoclinic crystals, a = 28.008(18), b = 6.114(3), c = 19.349(13) Å; β = 124.15(4), space group C2; Z = 8. The structure was solved by Patterson search with the program written by *P. B. Braun, J. Hornstra*, and *J. I. Leenhouts* (Philips Res. Rep. *24*, 85 (1969)) and refined with X-RAY 72 SYSTEM (Tech. Rep. TR-192. Computer Science Center, University of Maryland 1972) for 2240 reflections, R = 0.058 (Syntex P2$_1$ diffractometer, $Mo_{K\alpha}$, $2\theta_{max}$ = 47°).

[5] *K. B. Wiberg, G. J. Burgmaier, K. W. Shen, S. J. LaPlaca, W. C. Hamilton, M. D. Newton*, J. Am. Chem. Soc. *94*, 7402 (1972).

[6] The comparable distance in 8,8-dichlorotricyclo[3.2.1.0^{1,5}]octane is 0.093 Å [5].

[7] a) Bicyclo[1.1.0]butane: 1.497 Å; *K. W. Cox, M. D. Harmony, G. Nelson, K. B. Wiberg*, J. Chem. Phys. *50*, 1976 (1969); b) benzvalene: 1.452 Å; *R. D. Suenram, M. D. Harmony*, J. Am. Chem. Soc. *95*, 4506 (1973); c) 6-thiatetracyclo[5.4.0.0^{2,4}.0^{3,5}]undeca-1(7),8,10-triene: 1.483 Å; *C. Kabuto, T. Tatsuoka, I. Murata, Y. Kitahara*, Angew. Chem. *86*, 738 (1974); Angew. Chem. Int. Ed. Engl. *13*, 669 (1974); d) 1,5-diphenyltricyclo[2.1.0.0^{2,5}]pent-3-yl *p*-bromobenzoate: 1.44 Å; *J. Trotter, C. S. Gibbons, N. Nakatsuka, S. Masamune*, J. Am. Chem. Soc. *89*, 2792 (1967).

A Stable σ/π-Organometallic Radical of Vanadium: $(\eta^5\text{-}C_5Me_4Et)_2V\text{—}C{\equiv}C\text{—}C_6H_2Me_3$[**]

By *Frank H. Köhler, Wolfram Prössdorf, Ulrich Schubert*, and *Dietmar Neugebauer*[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

Vanadocenes bearing an additional σ-bonded organic group on the metal could provide valuable information about the still unknown V—C bond length[1, 11], about the stability of this bond, about *Hoffmann*'s MO concept of bent metallocenes[2], and about paramagnetic NMR behavior, if only it were possible to adequately stabilize these molecules, which are generally known to be unstable and poorly characterizable[3].

We have successfully stabilized such a molecule by peralkylation of the cyclopentadienyl ligands. Starting from 3-ethyl-1,2,4,5-tetramethylcyclopentadiene *(1)*[4], slight modifications to our previous synthesis[5] yield peralkylated vanadocene *(2)* and vanadocene bromide *(3)*. Reaction of *(3)* with the sodium salt of mesitylacetylene *(4)* gives olive-green, air-sensitive bis(ethyltetramethyl-η^5-cyclopentadienyl)mesitylethynylvanadium *(5)*. While the nonalkylated compound rapidly decomposes at 25 °C[6], compound *(5)* melts at 83—84 °C, can be sublimed (leaving a residue), and survives several hours' heating in boiling toluene without decomposition.

Elemental analysis and mass spectrum (principal metal-containing ions at 70 eV and 75 °C: M^+ (32), $[M+1]^+$ (12), $[M-(4)]^+$ (72), $[M+2-(1)]^+$ (100), $[M-(1)]^+$ (44), $[V\text{—}C{\equiv}C\text{—}C_6H_2Me_3]^+$ (20)) prove the composition of *(5)*; X-ray analysis[7] provides proof of its structure (cf. Fig. 1). The vanadium atom lies in the plane E1 (C20, M1, M2) and can be regarded as surrounded by three hydrocarbon groups in an almost trigonal-planar fashion. Peralkylation of the five-membered rings does not lead to any significant increase in the metal-ring distances compared with other $(\eta^5\text{-}C_5H_5)$-vanadium derivatives[8] studied so far; instead, the M1—V—M2 angle (149.7°) is considerably greater than that in $(\eta^5\text{-}C_5H_5)_2VCl$ (139.5°)[8b]. In spite of this decrease in strain, the methyl groups are bent out of the planes of the five-membered rings away from the vanadium by up to 32 pm. The bond angles and the bond lengths of the acetylene moiety are typical[9], whereas no reference data are available for the $V^{III}\text{—}C_{sp}$ distance of 203.2 pm.

Of particular interest was the question how the plane of the benzene ring E2 would be oriented relative to the coordination plane of the vanadium E1. With regard to the metal orbitals, and especially b_2, according to *Hoffmann et al.*[2] conjugation might conceivably extend from the vanadium to the benzene ring, which should lead to a parallel arrangement of E1 and E2. In contrast, we find these planes to enclose an angle of 86.8°. Thus π-interaction occurs only between V/C20/C201 on the one hand and between C20/C201/mesityl on the other.

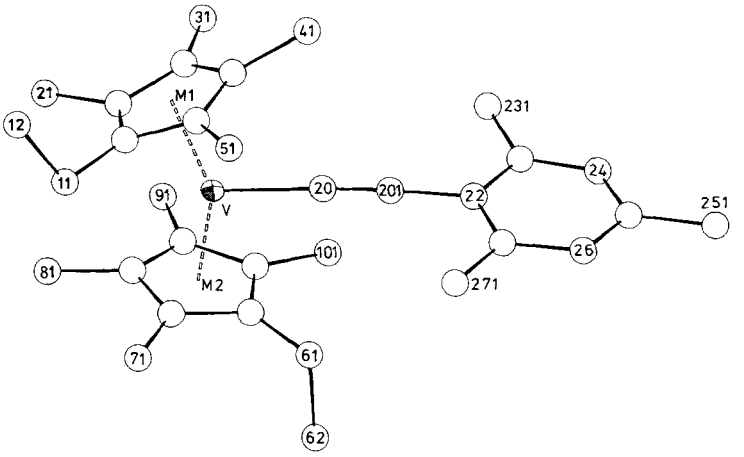


Fig. 1. Molecular structure of the organometallic radical *(5)*.

Distances	[pm]	Angles	[°]
V—M1	197.6	M1—V—M2	149.7 (1)
V—M2	197.0	M1—V—C20	105.4 (4)
V—C20	203.2 (13)	M2—V—C20	104.8 (4)
C20—C201	123.4 (17)	V—C20—C201	176.6 (10)
C201—C22	144.7 (14)	C20—C201—C22	175.5 (12)

A well-resolved paramagnetic ^{1}H-NMR spectrum can be recorded for *(5)*. It exhibits broad signals (300—400 and 120 Hz wide) having large chemical shifts such as are typical for protons located α or β to a cyclopentadienyl ring[5b]: $\delta^{para}(^1H\text{-}31/41/81/91)$[10] $= -22.3$, $\delta^{para}(^1H\text{-}21/51/71/101) = -18.2$, $\delta^{para}(^1H\text{-}11/61) = -10.3$, and $\delta^{para}(^1H\text{-}12/62) = +0.6$. In addition, signals of 20—80 Hz width are observed for the bonded acetylene: $\delta^{para}(^1H\text{-}24/26) = -20.5$, $\delta^{para}(^1H\text{-}231/271) = -10.1$, and $\delta^{para}(^1H\text{-}251) = -8.7$. On comparison with vanadocene halides[5b], these data show *(5)* to be an organometallic radical possessing two unpaired electrons and confirm that the vanadium is surrounded only by two π- and one σ-bonded hydrocarbon groups. Correlation of δ^{para} with the distance from vanadium shows that the delocalization of unpaired electrons is much more pronounced onto the acetylene than onto the π ligands. Thus, elucidation of structure and studies on electron distribution in radicals of the $(\eta^5\text{-}C_5H_5)_2V\text{—}R$ type are seen to be possible by NMR.

Procedure

Sodium mesitylacetylide (0.58 g, 3.5 mmol) is added to a solution of *(3)* (1.45 g, 3.4 mmol) in diethyl ether (50 ml). After removal of ether, the residue is extracted with pentane (30 ml), the olive-green extract treated with ethanol (30 ml), and the pentane removed under reduced pressure. Compound *(5)* crystallizes from the ethanol solution at −78 °C. Recrystallization from ethanol (2×) and from pentane (3×) gives lustrous black crystals of analytically pure *(5)* (0.35 g, 21 %).

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(3), 68185-51-3; *(4)*, 68184-34-9; *(5)*, 68185-52-4

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] *J. L. Atwood*, personal communication; *J. L. Atwood, W. E. Hunter, H. Alt, M. D. Rausch*, J. Am. Chem. Soc. *98*, 2454 (1976).

[2] *J. W. Lauher, R. Hoffmann*, J. Am. Chem. Soc. *98*, 1729 (1976).
[3] *H. J. de Liefde Meijer, M. J. Janssen, G. J. M. van der Kerk*, Rec. Trav. Chim. Pays-Bas *80*, 831 (1961).
[4] *D. Feitler, G. M. Whitesides*, Inorg. Chem. *15*, 466 (1976).
[5] a) *F. H. Köhler, W. Prössdorf*, Z. Naturforsch. *B32*, 1026 (1977; b) Chem. Ber. *111*, 3464 (1978).
[6] *J. H. Teuben, H. J. de Liefde Meijer*, J. Organomet. Chem. *17*, 87 (1969).
[7] At 243 K; cell: $a=1142.9(10)$, $b=1595.8(11)$, $c=1585.4(12)$ pm, $\beta=102.21(9)°$, $V=2826\cdot10^6$ pm^3, $\rho_{calc}=1.17$ g/cm^3; space group $P2_1/c$, $Z=4$. Syntex $P2_1$/XTL, $2\theta\leqslant45°$, $\lambda=71.069$ pm (graphite monochromator); 2016 structure factors, $F\geqslant5.4$ (F_0), $R_w=0.092$.
[8] a) Cf., *e.g. G. Engebretson, R. E. Rundle*, J. Am. Chem. Soc. *85*, 481 (1963); *E. G. Muller, J. L. Peterson, L. F. Dahl*, J. Organomet. Chem. *111*, 91 (1976), and references cited therein; b) *B. F. Fieselmann, G. D. Stucky*, J. Organomet. Chem. *137*, 43 (1977).
[9] Cf., *e.g. W. A. Spofford, P. D. Carfanga, E. L. Amma*, Inorg. Chem. *6*, 1553 (1967); *R. G. Davies, R. H. B. Mais, P. G. Owston*, J. Chem. Soc. *A1967*, 1750; *J. L. Atwood, M. Tsutsui, N. Ely, A. G. Gebala*, J. Coord. Chem. *5*, 209 (1976), and references cited therein.
[10] The numbers refer to the protons attached to the C atoms shown in Fig. 1. A negative sign of δ^{para} denotes a downfield shift; temperature 307 K; the analogous signal of $(\eta^5\text{-}C_5Me_4Et)_2Fe$ [4] and of *(4)* served as reference; assignment in accord with [5b].
[11] *Note added in proof:* A value of V—C ≈ 208 pm has just been found in tetramesitylvanadium — *T. Glowiak, R. Grobelny, B. Jezowska-Trzebiatowsky, G. Kreisel, W. Seidel, E. Uhlig*, J. Organomet. Chem. *155*, 39 (1978).

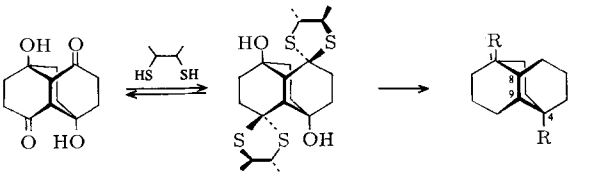
Optically Active Tricyclo[6.4.0.0^{4,9}]dodecane[**]

By *Hartmuth Buding* and *Hans Musso*[*]

Dedicated to Professor Hans Brockmann on the occasion of his 75th birthday

Chiral molecules not exhibiting measurable rotation are very rare (for examples see Ref.[1, 2]). According to the Brewster rules[3] the pure enantiomers of the title compound *(5)*—*(5a)* and *(5b)*—ought to be practically optically inactive. It was therefore of interest to prepare the enantiomers and to demonstrate their chirality.

The dihydroxydiketone *(1)*, recently shown to be readily accessible from furanophane[4], has the desired skeleton. The reaction of *(1)* with (−)-(*R*)-2,3-butanedithiol[5] affords a mixture of the diastereomeric dithioacetals *(2)*, which could be separated on silica gel using carbon tetrachloride/acetone (6:1). The first eluted *(2a)* (m.p. 99—101 °C) is clearly distinguishable from the more polar *(2b)* (m.p. 146—147 °C) by ^{1}H-NMR. In the presence of Eu(DPM)$_3$ a mutual contamination of >0.5 % can be ruled out from the signals of the methyl groups. Boiling of *(2a)* and *(2b)* with Raney nickel in methanol affords the alcohols *(3)* (m.p. 219—220 °C) in 60 % yield, which are converted by *Olah*'s method[6] into the bromides *(4)* (m.p. 149—150 °C) in 64 % yield. Dehalogenation is accomplished either with $LiAlH_4$ in dioxane or with tributyltin hydride (neat) to give the enantiomeric hydrocarbons *(5a)* and *(5b)* in 64 % yield (m.p. 47.5—49.0 °C) and having easily measurable optical rotations. A partial racemization was to be feared only in the transition *(3)*→*(4)*; the dibromides *(4)* obtained at 0 °C and +25 °C gave practically the same [α]-values. Neither the ^{1}H-NMR nor the mass spectrum revealed any olefinic contamination of *(5)*, which proved to be >99.6 % pure on VPC. The ^{13}C-NMR spectrum ($CDCl_3$)



(1) *(2)* *(3)*, R = OH; *(4)*, R = Br; *(5)*, R = H

	$[\alpha]_D^{20}$ *(a)*	*(b)*
(1)	—	−103.0° ± 5.0 (*c* = 0.12, dioxane)
(2)	−69.9°	+ 84.4° ± 0.4 (*c* = 0.52, $CHCl_3$)
(3)	−49.6°	+ 49.0° ± 0.4 (*c* = 2.02, CH_3OH)
(4)	−38.8°	+ 38.0° ± 0.4 (*c* = 2.04, $CHCl_3$)
(5)	−30.0°	+ 27.0° ± 2.0 (*c* = 0.23, cyclohexane)

is consistent with the structure *(5)* [δ = 21.1 (t), 27.8 (t), 32.3 (t), 34.2 (d; C-1, C-4), 36.3 (t), 36.7 (d; C-8, C-9)][7].

The dithioacetal *(2b)* afforded some optically active diketone *(1b)* (decomp. pt. 237 °C). The interaction of the carbonyl chromophores raises doubts concerning the validity of the octant rule in this special case. An X-ray structure analysis on *(1)*[4] has shown that all three cyclohexane rings exist in slightly twisted chair conformations. This has also been demonstrated by EFF calculations[8] for the minimum energy conformation of the hydrocarbon *(5)*, and this might be the reason for the unexpectedly high optical rotation.—The determination of the absolute configuration is being attempted.

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CAS Registry numbers:
(1), 68122-42-9; *(2a)*, 68122-43-0; *(2b)*, 68170-32-1; *(3a)*, 68122-44-1; *(3b)*, 68122-45-2; *(4a)*, 68122-46-3; *(4b)*, 68122-47-4; *(5a)*, 68122-48-5; *(5b)*, 68122-49-6; (−)-(*R*)-2,3-butanedithiol, 68170-33-2

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[2] *M. Bloch, N. Lau, H. Musso, U. I. Záhorszky*, Chem. Ber. *105*, 1790 (1972).
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[4] *H.-G. Fritz, H. Henke, H. Musso*, Chem. Ber. *107*, 3164 (1974).
[5] (+)-(*S*)-2,3-Butanediol, which is available from (+)-(*R*)-tartaric acid (*J. J. Plattner, H. Rapoport*, J. Am. Chem. Soc. *93*, 1758 (1971)) was converted into (−)-(*R*)-2,3-butanedithiol analogously to the method described by *E. J. Corey, R. B. Mitra*, J. Am. Chem. Soc. *84*, 2938 (1962).
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[7] Correct elemental analyses and spectra were obtained for all the new compounds.
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Template Reactions on Chromium(0): Synthesis of a Functionalized Indene from Pentacarbonyl[methoxy(phenyl)carbene]chromium and Bis(diethylamino)acetylene[1]

By *Karl-Heinz Dötz* and *Dietmar Neugebauer*[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

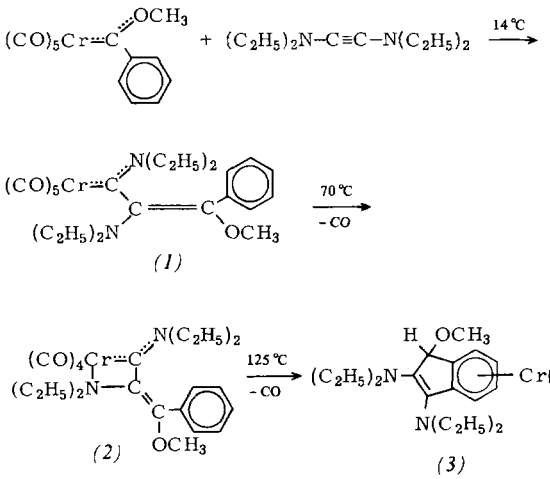
Carbene complexes of the type $(CO)_5MCR^1R^2$ react with nucleophilic alkynes such as ynamines and ynediamines at

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room temperature with insertion of the alkyne into the metal-carbene bond to give alkenyl(amino)carbene complexes[2]. *On warming* a typical representative of this class of compounds, pentacarbonyl[diethylamino(α-diethylamino-β-methoxystyryl)carbene]chromium *(1)*, in decane, a CO ligand *cis* to the carbene ligand is substituted intramolecularly by the amino function of the styryl substituent, leading to formation of the tetracarbonyl complex *(2)*. Stronger heating of the solution results in the loss of further CO and attack of the carbene-carbon at the *ortho* position of the phenyl ring. Thus cyclization occurs to give the 2,3-bis(diethylamino)-1-methoxyindene, which remains coordinated as the tricarbonyl complex *(3)* [^{1}H-NMR ([D$_6$]-acetone): δ = 5.53 (m, 4H, H-4,5,6,7), 5.05 (s, 1H, H-1), 3.64 (s, 3H, OCH_3), 4.07 and 3.09 (each m, 4H, NCH_2), 1.14 and 1.09 (each t, 6H, NCH_2CH_3); MS: M^+ at $m/e = 424$].



The ν(CO) IR spectrum (hexane: 1966, 1963; 1903, 1893, 1888 cm^{-1}) shows a double set of the expected absorption bands, indicating that the indene complex preferentially exists as two rotamers in solution (referred to the aromatic-metal axis). An X-ray structure analysis[3] of *(3)* confirmed the insertion of the ynediamine in positions 2 and 3 of the indene ring (Fig. 1). The bond lengths in the five-membered ring are 152(2) pm for C1—C2 and 137(2) pm for C2—C3. The oxygen atom O4 and the hydrogen atom H1 deviate significantly, 110 pm and 88 pm (difference Fourier calculation), respectively, from the C2, C3, N1, N2 plane, which is at an angle of 9° to the six-membered ring bound to the metal. The carbon atom C1 lies 5 pm above each of these two planes. The carbonyl groups are staggered relative to the carbon atoms coordinated to the metal, which are coplanar.

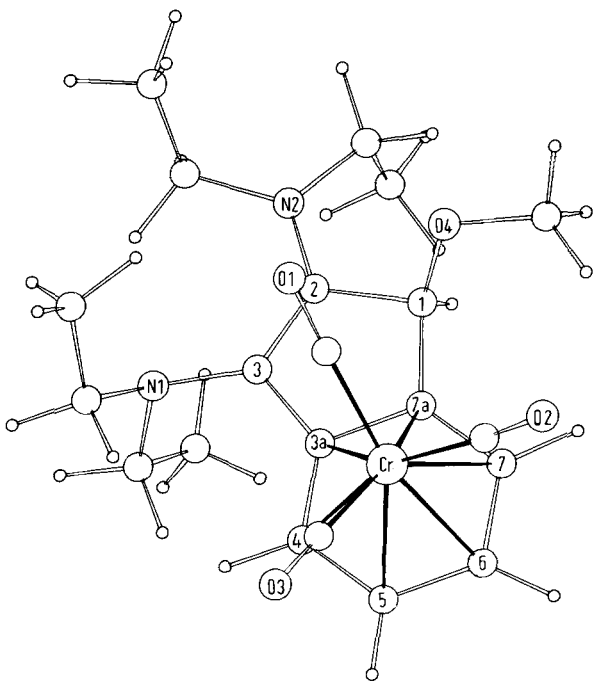


Fig. 1. Crystal structure of the complex *(3)*.

Under the same conditions the corresponding methoxy(phenyl)carbene complex of the higher homolog tungsten reacts with the ynediamine only up to the tetracarbonyl stage. The cyclization to the indene skeletal structure and the accompanying 1,3 hydrogen shift from the *ortho* position of the phenyl ring to the original carbene-carbon must therefore be ascribed to the influence of the chromium, which may be regarded as the active center of a template reaction.

Procedure

All work must be carried out under N_2 with dry (Na) solvents saturated with N_2.—A solution of *(2)*[2a] (0.40 g, 0.885 mmol) in decane (10 ml) is heated at 125 °C for 2 h. The color of the solution becomes paler, finally being yellow. After removal of solvent the residue is chromatographed on silica gel (Merck Act. 2—3) with benzene/pentane (2:1). The main zone affords yellow crystals of *(3)*, m.p. 64 °C, in 75% yield (0.28 g).

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(1), 60085-05-4; *(2)*, 60101-83-9; *(3)*, 68122-27-0; $(CO)_5CrC(OMe)(Ph)$, 27436-93-7; $(C_2H_5)_2N-C\equiv C-N(C_2H_5)_2$, 5323-13-7

[1] Reactions of Complex Ligands, Part 14. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 13: *K. H. Dötz, R. Dietz*, J. Organomet. Chem. *157*, C55 (1978).
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[3] 1318 structure factors ($I \geq 5.2\sigma$, Syntex $P2_1/XTL$, $\sin\theta/\lambda = 0.5723$), $\lambda = 71.069$ pm, $R_1 = 0.067$; monoclinic, space group $P2_1/c$, $Z = 4$, $a = 1843(2)$, $b = 1222(2)$, $c = 1944(2)$ pm, $\beta = 150.78(8)°$, $V = 2138.0 \times 10^6$ pm^3.

PdTeI and Pd_2SeI_3 – The First Chalcogenide Halides of a Platinum Metal[**]

By *Gerhard Thiele, Maria Köhler-Degner, Kurt Wittmann*, and *Gerd Zoubek*[*]

The chalcogenide halides of the coinage metals copper, silver, and gold have been the subject of intensive recent work owing to their interesting physical properties[1]. It seemed an obvious step to extend these studies to corresponding compounds of the platinum metals. However, all attempted preparations yielded only polycrystalline material contaminated with varying amounts of the binary halides and chalcogenides. The structures and precise composition of the new compounds therefore remained unknown. We now report the synthesis and structure analysis of the palladium compounds PdTeI and Pd_2SeI_3.

The ternary compounds can be prepared directly from the elements by low-pressure hydrothermal synthesis[2] in HI solu-

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tion. However, single crystals of Pd_2SeI_3 were obtained on reaction of PdI_2 with Se in liquid iodine.

In the brass-yellow crystals of PdTeI, the Te and I atoms are cubic close packed with Pd atoms occupying half of the octahedral vacancies. There is a close relationship to the NaCl type, which can also be substantiated by group theoretical considerations. The $PdTe_{2/2}I_{4/4}$ octahedra are stretched along the c axis (Pd—I 260 and 284, Pd—Te 284 pm, each $2\times$). They are linked alternately *via* edges of two I and two Te atoms to form chains. Since each I atom also represents the apex of two octahedra from adjacent layers, a loose three-dimensional network is formed (cf. Fig. 1). There are no covalent bonds between the Te and I atoms (closest contacts: I—I 339, Te—Te 380, Te—I 391 pm), and the compound should therefore be formulated as palladium(III) telluride iodide $Pd^{3+}Te^{2-}I^-$. The stretching of the coordination octahedron around Pd^{3+} can be explained as Jahn-Teller distortion of a d^7 low spin system. The diamagnetism, the good electrical conductivity (specific resistance at 25°C: $\rho = 4\times10^{-4}\,\Omega$ cm), and the striking color of the compound suggest, however, that the bonding can only be fully explained by the band model.

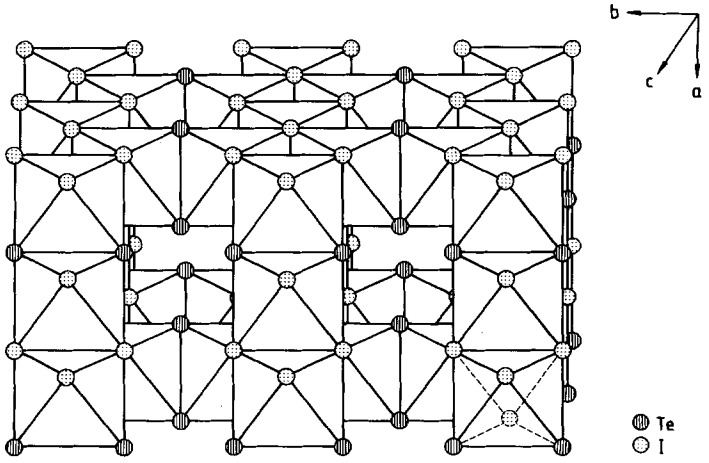


Fig. 1. Linkage of $PdTe_{2/2}I_{4/4}$ octahedra in the tetragonal unit cell of PdTeI [$a = 780.8(2)$, $c = 566.0(1)$ pm; space group $P4_2/mmc$; $Z = 4$].

In the metallic black rhomboid crystals of Pd_2SeI_3, however, Pd is in the formal oxidation state of +2, since in the orthorhombic unit cell the Pd atoms are in a square-planar environment of three I atoms and the Se atom of a Se_2 group. The Se_2^{2-} group links four such squares to form $Pd_4Se_2I_4I_{4/2}$ units (cf. Fig. 2), which in turn are linked *via* the four corners to form puckered layers.

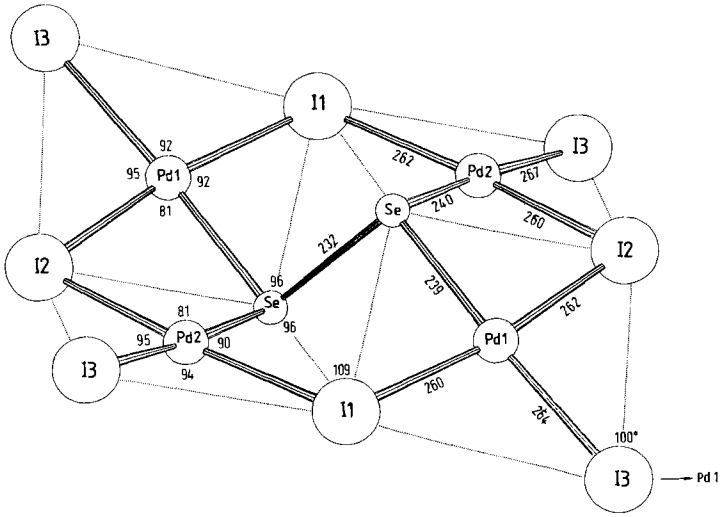


Fig. 2. $Pd_4Se_2I_4I_{4/2}$ structural units in Pd_2SeI_3 with principal distances and angles. The orthorhombic unit cell [$a = 791.1(1)$, $b = 1288.5(3)$, $c = 1432.1(3)$ pm; space group Pbca] contains 8 formula units.

Procedure

Single crystals of PdTeI: Pd sponge (50 mg), Te powder (60 mg), I_2 (120 mg), and KI (30 mg) are heated to 300°C with 55% HI solution (1 ml) for 6 d in a glass ampoule of *ca.* 4 ml capacity. The resulting brass-yellow crystalline needles were filtered off and washed several times with hot water (yield *ca.* 120 mg).

Single crystals of Pd_2SeI_3: PdI_2 (30 mg), Se (120 mg), and I_2 (7.5 g) are heated together to 250°C for 2 d in a glass ampoule, and the melt is slowly cooled (0.5°C/h) to just above the melting point of iodine. Liquid iodine is decanted from the precipitate within the ampoule; residual I_2 can be removed by repeated washing with acetone, and excess Se by heating with conc. H_2SO_4. Powder samples can be prepared more easily by reaction of Pd (70 mg), Se (52 mg), and I_2 (84 mg) in 1 ml of 55% HI solution.

X-ray structural data were recorded with $Mo_{K\alpha}$ radiation between 3° and 25° in a single crystal diffractometer. 229 (PdTeI) and 324 (Pd_2SeI_3) independent data were employed in the solution (program system SHELX[3]); refinement led to $R = 5.42$ and 8.33%, respectively.

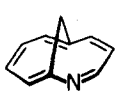
Received: July 31, 1978 [Z 69 IE]
German version: Angew. Chem. *90*, 897 (1978)

[1] *J. Fenner, D. Mootz*, J. Solid State Chem. *24*, 367 (1978); *U. v. Alpen, J. Fenner, B. Predel, A. Rabenau, G. Schluckebier*, Z. Anorg. Allg. Chem. *438*, 5 (1978); *P. M. Carkner, H. M. Haendler*, J. Solid State Chem. *18*, 183 (1976); references cited therein.
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[3] *G. Sheldrick*, University Chemical Laboratory, Cambridge UK 1976, Cyber 172 Version by *G. Zoubek*, Erlangen.

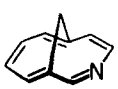
Bridged Aza[10]annulenes—10π-Analogues of Pyridine[**]

By *Maria Schäfer-Ridder, Arwed Wagner, Michael Schwamborn, Helmut Schreiner, Eveline Devrout, and Emanuel Vogel*[*]

The potentially aromatic monoaza[4n+2]annulenes—the homologues of pyridine—are still virtually unknown[1–3]. In view of the remote chance of being able to isolate simple aza[10]- and aza[14]annulenes we concentrated our efforts from the very beginning on the synthesis of the two bridged aza[10]annulenes, 2,7-methanoaza[10]annulene *(1)* and 3,8-methanoaza[10]annulene *(2)*, derived from 1,6-methano[10]annulene. Though earlier attempts to prepare these



(1)



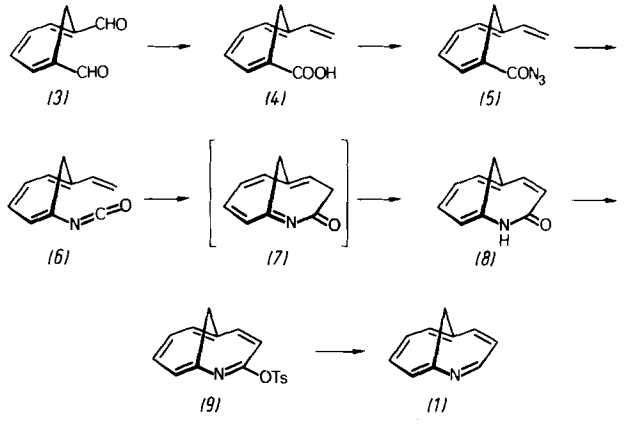
(2)

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novel heterocycles met without success[4], we have now found routes to *(1)* and to a derivative of *(2)*.

As starting compound for the synthesis of *(1)* we used cycloheptatriene-1,6-dicarbaldehyde *(3)*[5]. Reaction of *(3)* with methylene(triphenyl)phosphorane [prepared from $MePh_3PBr$ and $NaN(SiMe_3)_2$] in the molar ratio 1:1.25 in tetrahydrofuran (room temperature, 4 h) and subsequent chromatographic separation on silica gel (dichloromethane/hexane 1:1) afforded 6-vinyl-1,3,5-cycloheptatriene-1-carbaldehyde (40%), which on account of its sensitivity towards oxygen was immediately oxidized with aqueous alkaline silver oxide to the corresponding acid *(4)* [m.p. 116°C (from hexane); yield 82%; ^{1}H-NMR ($CDCl_3$): $\delta = 2.87$ (s, 2H, H-7), 5.27 (d, 1H), 5.87 (d, 1H), 6.48 (m, 1H) (ABX system of the vinyl protons), 6.2–7.0 (m, 3H, H-3, 4, 5), 7.43 (d, 1H, H-2), 11.0 (br. s, 1H, COOH); UV (cyclohexane): $\lambda_{max} = 238$ nm ($\varepsilon = 33000$), 292 (2650), 343 (5000)]. The acid azide *(5)* formed on reaction of the acid chloride of *(4)* with sodium azide in aqueous acetone undergoes Curtius rearrangement on heating in toluene (110°C, 30 min) to give 6-vinyl-1,3,5-cycloheptatrienyl 1-isocyanate *(6)*, a compound isolable under these conditions but prone to polymerize (b.p. 30°C/0.1 torr).



(3) *(4)* *(5)* *(6)* *(7)* *(8)* *(9)* *(1)*

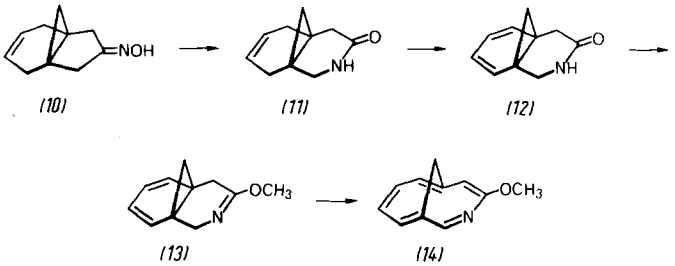
The supposition that the isocyanate *(6)* could isomerize thermally by a 10π-electrocyclic process[6]—or by successive cycloheptatriene-norcaradiene and Cope rearrangements[7]—to the azaenone *(7)*, and that *(7)* could readily be converted prototropically into the thermodynamically more stable lactam *(8)* (2-azabicyclo[4.4.1]undeca-4,6,8,10-tetraen-3-one) has been confirmed experimentally: on heating *(6)*, or better the acid azide *(5)*, for 12 h in toluene the expected lactam *(8)* is formed as main product [yellow needles, m.p. 143–144°C (from ethyl acetate); yield 35% based on *(4)*; ^{1}H-NMR ($CDCl_3$): $\delta = 0.17$ and 1.85 (AX system, $J = 9.6$ Hz, 2H, H-11), 6.17 (d, $J = 11.4$ Hz, 1H, H-4), 6.5–7.4 (m, 4H, H-7, 8, 9, 10), 7.54 (d, $J = 11.4$ Hz, 1H, H-5), 11.7 (br. s, 1H, NH); UV (acetonitrile): $\lambda_{max} = 223$ nm ($\varepsilon = 12700$), 270 (28800), 302 (4700), 373 (3500); IR ($CHCl_3$): 3380, 1620 cm^{-1}].

Analogous to α-pyridone, *(8)* on reaction with trimethyloxonium tetrafluoroborate in dichloromethane (room temperature, 4 h) or on reaction of its silver salt with methyl iodide, experiences almost exclusive *O*-alkylation to 10-methoxy-2,7-methanoaza[10]annulene [bright yellow liquid, b.p. 60–61°C/0.1 torr; yield 54% and 55%, resp.; ^{1}H-NMR ($CDCl_3$): $\delta = 0.22$ and 0.4 (AB system, $J = 9.0$ Hz, 2H, H-11), 4.0 (s, 3H, OCH_3), 6.06 (d, $J = 10.2$ Hz, 1H, H-9), 6.7–7.3 (m, 4H, H-3, 4, 5, 6), 7.47 (d, $J = 10.2$ Hz, 1H, H-8); UV (cyclohexane): $\lambda_{max} = 236$ nm ($\varepsilon = 21500$), 264 (26000), 294 (sh, 5300), 372 (4700)], while with diazomethane a mixture of comparable amounts of *O*- and *N*-methylation products is obtained.

Attempts were made to accomplish the transformation of *(8)* into *(1)* *via* the *O*-tosyl derivative *(9)* [prepared from the potassium salt of *(8)* and *p*-toluenesulfonyl chloride in tetrahydrofuran (room temperature, 1 h), bright yellow needles, m.p. 82–83°C (from methanol); yield 78%]. Reduction of *(9)* with two equivalents of lithium aluminum hydride in boiling tetrahydrofuran (30 min) afforded an unstable product in which, according to ^{1}H-NMR analysis, a mixture of dihydro compounds of *(1)* was present. Consistent with this finding, treatment of the original reaction mixture with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (room temperature, 10 min) led to dehydrogenation of the reduction product and formation of a nitrogen base, which could be isolated in pure form (yield 36–40%) by chromatographic filtration on aluminum oxide followed by distillation. As confirmed spectroscopically, this compound, a stable yellow liquid of b.p. 63°C/1 torr and having a quinoline-like odor, is the desired 2,7-methanoaza[10]annulene *(1)*.

The most convincing evidence for the structure of *(1)* and for its aromatic character is provided by the ^{1}H-NMR spectrum [90 MHz (CCl_4): $\delta = -0.4$ and 0.65 (AX system, $J = 8.4$ Hz, 2H, H-11b, and H-11a[8]), 6.5 (dd, $J = 9.0$ and 6.3 Hz, 1H, H-9), 6.6–7.2 (m, 3H, H-4, 5, 6), 7.38 (two superposing doublets, 2H, H-3, 8), 8.23 (d, $J = 6.3$ Hz, 1H, H-10)], for it combines the characteristics of the spectra of α-substituted 1,6-methano[10]annulenes and of pyridine and quinoline. Striking similarities to the spectra of the 1,6-methano[10]annulenes are seen not only in the position of the resonances of annulene- and bridge-protons at low field and high field, respectively, but also in the coupling constants of the bridge protons [$J_{H\text{-}11a,H\text{-}11b} = 8.4$ Hz, $J_{^{13}C\text{-}11,H\text{-}11} = 145$ Hz (142 Hz in the case of 1,6-methano[10]annulene)]. Very good agreement is also found in the absorption patterns of the annulene protons of *(1)* and the quinoline protons; however, in parallel with the findings in the pair 1,6-methano[10]annulene/naphthalene, the resonances of the annulene protons appear at higher field.—That *(1)* is to be regarded as a heteroaromatic system is equally evident from the similarity of its UV spectrum [(cyclohexane): $\lambda_{max} = 240$ nm ($\varepsilon = 28300$), 258 (11800), 297 (sh, 2650), 364 (2200)] with that of 1,6-methano[10]annulene; qualitative differences between the two spectra, such as the increased extinction of the long-wave L_b band in the azaannulene spectrum, correspond to those observed between the naphthalene and the quinoline spectrum.

The aza[10]annulene *(1)* has a pK_a value of 3.20 (20°C) and is thus more weakly basic than pyridine or quinoline ($pK_a = 5.23$ and 4.94, respectively)[9]; nevertheless, it forms a stable hydrochloride with dry hydrogen chloride in ether.



(10) *(11)* *(12)* *(13)* *(14)*

Parallel to the synthesis of *(1)* we tried to prepare the isomeric 3,8-methanoaza[10]annulene *(2)* starting from tricyclo[4.3.1.0]deca-3-en-8-one oxime *(10)*[4]. Beckmann rearrangement of *(10)* with phosphorus pentachloride in ether

(0 °C, 5 h) led to the lactam *(11)* [m.p. 93–94 °C; yield 48%], which, on addition of bromine in dichloromethane and subsequent dehydrohalogenation of the resulting dibromide (not isolated) with 1,5-diazabicyclo[4.3.0]non-5-ene in tetrahydrofuran (room temperature, 15 h), could be transformed into the lactam *(12)* present as the norcaradiene valence tautomer [m. p. 128–129 °C; yield 30%; ^{1}H-NMR ($CDCl_3$): $\delta = -0.18$ and 1.71 (AX system, $J = 4.2$ Hz, 2H, H-11), 2.71 (q, $J = 17$ Hz, 2H, H-5), 3.44 (d, $J = 13$ Hz, 1H, one H-2), 3.69 (dd, $J = 13$, and 5 Hz, 1H, one H-2), 5.8 (m, 4H, H-7, 8, 9, 10), 6.9 (br. s, 1H, NH)].

(12) reacts with trimethyloxonium tetrafluoroborate in dichloromethane (room temperature, 4 h) with formation of the iminoether *(13)*, also present as the norcaradiene valence tautomer [b.p. 64–66 °C/0.1 torr; yield 50%; ^{1}H-NMR ($CDCl_3$): $\delta = -0.25$ and 1.44 (AX system, $J = 4.2$ Hz, 2H, H-11), 2.52 (q, $J = 17$ Hz, 2H, H-5), 3.53 (s, 3H, OCH_3), 3.83 (q, $J = 16$ Hz, 2H, H-2), 5.92 (m, 4H, H-7, 8, 9, 10)]. Dehydrogenation of *(13)* with DDQ in dioxane (room temperature, 1 min) led to a complex reaction mixture, from which 10-methoxy-3,8-methanoaza[10]annulene *(14)* could be isolated by chromatography on silica gel (ether/pentane 1:3) as a stable yellow liquid of b.p. 62–63 °C/0.1 torr (yield 4–8%) [^{1}H-NMR (CCl_4): $\delta = -0.14$ and 0.37 (AX system, $J = 9.5$ Hz, 2H, H-11), 3.86 (s, 3H, OCH_3), 5.90 (s, 1H, H-9), 6.66 and 7.28 (multiplet, 4H, H-4, 5, 6, 7), 7.46 (s, 1H, H-2)].

The NMR spectrum of this 3,8-methanoaza[10]annulene derivative, which corresponds to that of the isomeric 10-methoxy-2,7-methanoaza[10]annulene, affords clear evidence of this system also being aromatic[10].

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CAS Registry numbers:
(1), 64183-86-4; *(2)*, 64183-85-3; *(3)*, 28172-94-3; *(4)*, 68050-77-1; *(5)*, 68050-78-2; *(6)*, 68050-79-3; *(7)*, 68050-80-6; *(8)*, 68050-81-7; *(8)*, silver salt, 68050-82-8; *(8)*, potassium salt, 68050-83-9; *(9)*, 68050-84-0; *(10)*, 68050-85-1; *(11)*, 68050-86-2; *(12)*, 67338-10-7; *(13)*, 68050-87-3; *(14)*, 66910-93-8; 6-vinyl-1,3,5-cycloheptatriene-1-carbaldehyde, 68050-88-4; 10-methoxy-2,7-methanoaza[10]annulene, 68050-89-5

[1] The synthesis of 10-methoxy-2,7-methanoaza[10]annulene by *O*-methylation of the lactam *(8)* was first reported by *E. Vogel* at the 3rd International Symposium on Novel Aromatic Compounds (ISNA 3), San Francisco (USA), August 1977.

[2] An aromatic bridged monoaza[14]annulene, *trans*-1,3-10b,10c-tetramethyl-10b,10c-dihydro-2-azapyrene has been described by *V. Boekelheide* and *W. Pepperdine*, J. Am. Chem. Soc. *92*, 3684 (1970).

[3] For the synthesis of aza[$4n+1$]annulenes, which are to be regarded as homologues of pyrrole, see *A. G. Anastassiou*, Pure Appl. Chem. *44*, 691 (1975); *G. Schröder*, *ibid. 44*, 925 (1975).

[4] *E. deCleur*, Diplomarbeit, Universität Köln 1967.

[5] *E. Vogel*, *R. Feldmann*, *H. Düwel*, Tetrahedron Lett. *1970*, 1941.

[6] The analogous 6π-electrocyclic process, the thermal isomerization of butadienyl-1-isocyanates to α-pyridones, has been reported: *L. E. Overman*, *S. Tsuboi*, J. Am. Chem. Soc. *99*, 2813 (1977); and references cited therein.

[7] Cf. also the Cope rearrangement of *cis*-2-vinylcyclopropyl isocyanate: *E. Vogel*, *R. Erb*, *G. Lenz*, *A. A. Bothner-By*, Justus Liebigs Ann. Chem. *682*, 1 (1965).

[8] H-11a corresponds to the proton above the carbocyclic ring segment; assignment of the two bridge protons is based on long-range coupling.

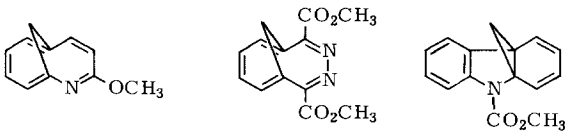
[9] *A. Albert* in *A. R. Katritzky*: Physical Methods in Heterocyclic Chemistry, Vol. 1. Academic Press, New York 1963, p. 65.

[10] We decided to publish the investigations on *(2)* earlier than planned, on learning that 10-ethoxy-3,8-methanoaza[10]annulene has been synthesized independently by *Muchowski et al.* in almost the same way as *(14)*; *H. J. Gölz*, *J. M. Muchowski*, *M. L. Maddox*, Angew. Chem. *90*, 896 (1978); Angew. Chem. Int. Ed. Engl. *17*, 855 (1978). *Note added in proof* (October 20, 1978): Meanwhile, it has come to our attention that 10-methoxy-3,8-methanoaza[10]annulene *(14)* has also been prepared *G. K. Helmkamp*'s group (University of California, Riverside) [*W. J. Lipa*, Diss. Abstr. Int. B *38* (9), 4243 (1978)].

10-Ethoxy-3,8-methanoaza[10]annulene, a 10π-Electron Analogue of Pyridine[**]

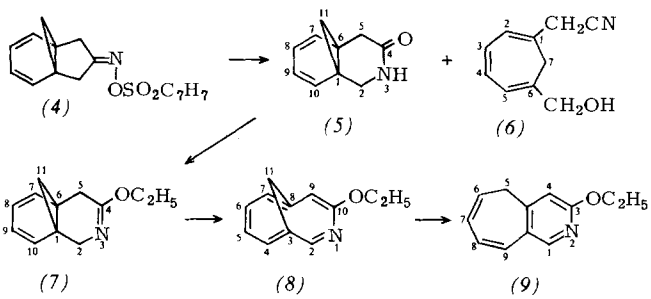
By *Hans-Jürgen Gölz*, *Joseph M. Muchowski*, and *Michael L. Maddox*[*]

The synthesis of 1,6-methano[10]annulene, a hydrocarbon which contains a delocalized 10π-electron system, was reported almost 15 years ago by *Vogel* and *Roth*[1]. In principle, it should be possible to prepare analogues of this compound where one or more heteroatoms participate in the establishment of a 10π-system stabilized by resonance, and indeed, three such compounds *(1)*—*(3)* with potential 10π-systems have been synthesized. Whereas the recently disclosed methanoaza[10]annulene derivative *(1)*[2] possesses spectral properties consistent with those expected for an aromatic system, *(2)* and *(3)* do not. Thus, *(2)* is best regarded as a fluxional molecule[3a], while *(3)* definitely exists in the norcaradiene form[3b]. This publication describes the synthesis of the title compound *(8)*, a methanoaza[10]annulene derivative[4], whose skeleton is isomeric with that present in *(1)*.



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

The *O*-(*p*-toluenesulfonyl) oxime *(4)* (m.p. 115–117 °C)[5], obtained from the corresponding known oxime[6] and *p*-toluenesulfonyl chloride, when heated (40 °C, 3 d) in aqueous dioxane in the presence of 2,6-dimethylpyridine, gave the products of Beckmann rearrangement *(5)* and fragmentation *(6)* in 20—30% and 17% yields, respectively (Table 1). The lactam *(5)* was converted with triethyloxonium tetrafluoroborate (CH_2Cl_2, room temperature, 5 d) into the cyclic imino ether *(7)* which on dehydrogenation with dichlorodicyanoquinone (dioxane, room temperature, 0.5—2 h) gave 10-ethoxy-3,8-methanoaza[10]annulene *(8)* in 8.5—13.5% yield. Compound *(8)*, a stable yellow oil, was isolated by preparative thin-layer chromatography (hexane/ethyl acetate, 10:1, silica gel). The UV spectrum of *(8)* (Table 1) is indicative of a system with extended conjugation, while the low field ^{1}H-NMR signals of the OCH_2- and perimeter-protons, in conjunction with the upfield shift of the hydrogens in the methano bridge, are compatible with the existence of a ring current in the 10-atom periphery. The proton-decoupled ^{13}C-NMR



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

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

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spectrum (Table 1) is also consistent with the presence of a delocalized π-system in *(8)*.

On prolonging the duration of the dehydrogenation of *(7)* from 2 to 22 h, the annulene *(8)* (6—7 %) was accompanied by variable amounts (11—16 %) of 3-ethoxy-5*H*-cyclohepta[*c*]pyridine *(9)*[7], which was separated by thin-layer chromatography (hexane/ethylacetate, 10:1) (Table 1). The isomerization *(8)* → *(9)* could proceed analogously to the rearrangement of 1-benzoxepin[8]. Finally, it is also of interest that the mass spectra of *(8)* and *(9)* are identical [*m/e* 187 (M^+, 66 %)], implying the electron impact induced transformation of the former into the latter.

Table 1. Physical data of compounds *(5)*—*(9)*.

(5), m.p. 126—128 °C; IR (KBr): 3190, 1670 cm^{-1}; ^{1}H-NMR [a]: −0.12 [b], 1.73 (q, J=4, 11-CH_2), 2.73 (q, J=17, 5-CH_2), 3.59 (q, J=14, 2-CH_2), 5.84 (s, 7-H to 10-H), 7.20 (br., NH)

(6), b.p. 80—85 °C/0.2 torr; IR ($CHCl_3$): 3600, 3420, 2250 cm^{-1}; ^{1}H-NMR [a]: 2.40 (s, 7-CH_2), 2.96 (s, OH), 3.30 (s, CH_2CN), 4.14 (s, CH_2O), 6.10 (m, 2H), 6.44 (m, 2H)

(7), b.p. 70—75 °C/0.1 torr; ^{1}H-NMR [a]: −0.17 [b], 1.50 (q, J=4, 11-CH_2), 1.20 (t, J=6, CH_3), 2.50 (q, J=16, 5-CH_2), 3.80 (q, J=16, 2-CH_2), 3.97 (q, J=6, OCH_2), 5.83 (m, 7-H to 10-H)

(8), b.p. 70 °C/0.1 torr; UV (CH_3OH): λ_{max}=258 nm (ε=20400), 315 (3650); ^{1}H-NMR [a]: 0.00, 0.54 [b] (q, J=10, 11-CH_2), 1.40 (t, J=7, CH_3), 4.37 (q, J=7, OCH_2), 5.94 (s, W_H=5, 9-H), 6.55, 7.20 (m, 4-H to 7-H), 7.44 (s, W_H=5, 2-H); ^{13}C-NMR [a]: 14.79 (CH_3), 33.84 (C-11), 61.35 (OCH_2), 100.62 (C-9), 123.96 (C-5), 124.84 (C-3), 125.29 (C-8), 127.99 (C-6), 130.33 (C-7), 131.27 (C-2), 157.02 (C-10) [c].

(9), b.p. 110 °C/0.05 torr; UV (CH_3OH): λ_{max}=224 nm (ε=6300), 293 (2950); ^{1}H-NMR [a]: 1.33 (t, J=7, CH_3), 3.02 (d, $J_{5,6}$=6.3, 5-CH_2), 5.75—6.13 [d] (9 lines, $J_{5,6}$=6.3, $J_{6,7}$=10.0, $J_{7,8}$=5.9, 6-H, 7-H), 6.51 (q, $J_{7,8}$=5.9, $J_{8,9}$=11.5, 8-H), 6.87 (d, $J_{8,9}$=11.8, 9-H); ^{13}C-NMR [a]: 14.79 (CH_3), 30.40 (C-5), 61.74 (OCH_2), 107.90 (C-4), 126.30, 129.84, 131.50, 132.41 (C-6 bis C-9), 144.89 (C-1, C-9a), 145.90 (C-4a), 162.64 (C-3)

[a] NMR spectra ($CDCl_3$), δ values, TMS intern. ^{1}H-NMR spectra: Varian T-60 and HA-100 spectrometers, J in [Hz]; ^{13}C-NMR spectra: Bruker WH-90 Pulse Fourier Transform spectrometer.

[b] Closely spaced multiplets because of long range coupling.

[c] The low intensity of this absorption makes the assignment uncertain. A weak signal was also present at δ=164.86. For 2-methoxypyridine, C-2 is found at δ=163.1.

[d] Measured at 100 MHz, complete analysis of the cycloheptatriene protons with a LACON 3 computer program [9] modified for use on an IBM 1800 as well as ITRACAL (Nicolet Instruments Corp., Madison, Wisconsin, 1973) operating on a Nicolet BNC-12.

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[4] The methoxy compound analogous to *(8)* has been independently synthesized by *E. Vogel et al.*; cf. [2b]. We thank Professor *Vogel* for providing us with this information prior to publication.

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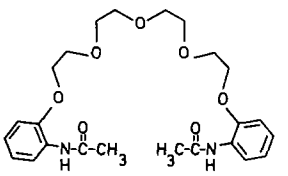
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Wrapping of Noncyclic Donor Molecules around the Sodium Cation

By *Jean Grandjean, Pierre Laszlo, Fritz Vögtle*, and *Heinz Sieger*[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

Heptadentate ligands such as the noncyclic crown ether *(1)* are good complexing agents for alkali metal and alkaline earth cations[1]. A crystalline 1:1 complex is obtained between *(1)*[2a] and KSCN[2b]. However, the formation of well-defined complexes does not necessarily reflect the size of the formation constant (K_f) for the complex[2b, 3]. Whereas reactions of charged ligands with metal ions of type A are *entropy*-driven, interactions of uncharged ligands with the soft metal ions of type B are preferably *enthalpy*-driven[3]. Still requiring clarification, however, was the mode of reaction of uncharged open chain ligands such as *(1)* with unpolarized A-type metals. We report here on the determination of the thermodynamic parameters for complexation of *(1)* with the sodium cation by ^{23}Na-NMR spectroscopy[4].



(1)

The ligand *(1)* containing two carboxamide groups competes with the likewise powerful complexing agent pyridine chosen as solvent. For the ^{23}Na-NMR measurements, *(1)* and anhydrous $NaClO_4$ were co-dissolved in anhydrous pyridine[5]. The correlation times are sufficiently small: the NMR absorption curves are true lorentzians and their linewidths at half-height are inversely proportional to the temperature[6]. K_f was determined by the following procedure[4, 6, 7]:

Line broadening
↓
Relaxation rate R
↓
R normalized to unit viscosity R_v
↓
Measurement of R_v as a function of composition (5 or 6 data points)
↓
Computer fitting of parameters to 1:1 complex model

Two separate methods are used for the last step (see Figure 1 and Table 1).

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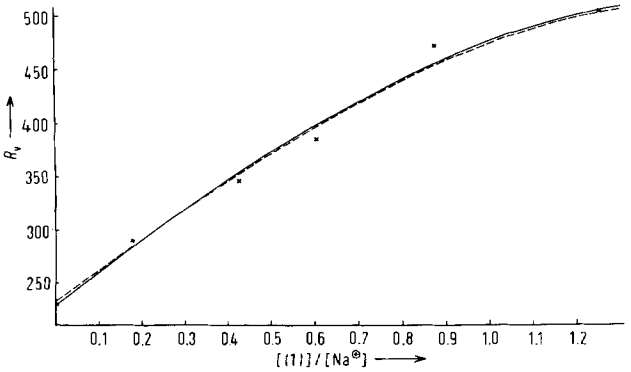


Fig. 1. Plot of R_v *versus* $[(1)]/[Na^+]$ (32 °C = 305 K); the solid line (method A) is the curve for minimization of R_v for each of 5 experimental points (×), corresponding to iteration of the values for K_f and the limiting relaxation rate in the complex from *(1)* and $Na^{\oplus}$ (equation (2) of reference [6a]). The dashed line (method B) corresponds to Simplex optimization [8a] using the equation of *Live* and *Chan* [8b] with simultaneous iteration on K_f, R_v^B, and the relaxation rate for free $Na^{\oplus}$ R_v^F.

Table 1. Complexation constant K_f and limiting relaxation rates for free (R_v^F) and bound (R_v^B) $Na^{\oplus}$ obtained by method A and method B.

T[K]	R_v^F		R_v^B		K_f [l mol^{-1}]	
	A	B	A	B	A	B
279.2	229	223	848	861	750	749
290.6	229	226	691	691	240	241
305.2	229	232.5	575	565.5	75	77.5
321.5		195		600		12.2

A strong complex is indeed formed between *(1)* and $NaClO_4$, in pyridine solution, with a formation constant K_f of 10^3 to 101 mol^{-1} in the temperature range from 5 to 50 °C. From the temperature dependence of K_f it follows that:

$\Delta H_f^0 = -17$ kcal mol^{-1} (-71 kJ mol^{-1}[9])
$\Delta S_f^0 = -48$ cal mol^{-1} K^{-1} (-201 J mol^{-1} K^{-1}[9]).

Usually, only mildly negative entropy terms (*ca.* -10 to -50 J mol^{-1} K^{-1}[10]) are found for inclusion of $Na^{\oplus}$ into the preformed central cavities of cyclic natural or synthetic ionophores in solvents such as H_2O or CH_3OH. It is unlikely that only the change from such protic solvents to pyridine could account for this large difference in complexation entropies. Rather, the strongly negative entropy term found here is highly reminiscent of a *cyclization entropy*, as if $Na^{\oplus}$ complexation locks the ligand molecule *(1)* into a single highly organized conformation: one in which most (if not all)[11] the ether oxygens form van der Waals bonds with the enclosed sodium cation, accounting for the magnitude of the enthalpy change. The complex formation in solution is *enthalpy*-driven. The $Na^{\oplus} - ClO_4^{\ominus}$ distance is likely to increase upon complex formation[6b]. Hence, we feel that the interaction of *(1)* and $Na^{\oplus}$ is best described as a *wrapping* of the heptadentate ligand *(1)*, most probably in a stepwise manner[10c], around the sodium cation. Pyridine, a weakly polar aprotic solvent capable of cation solvation, is a solvent of type B in the recent classification by *Jackman* and *Lange*[12]. From the relatively large equilibrium constants K_f found in pyridine, we feel confident that molecules of the same type as *(1)*[2b] will produce *anionic activation* in a number of organic solvents of type B[12], particularly at low temperatures.

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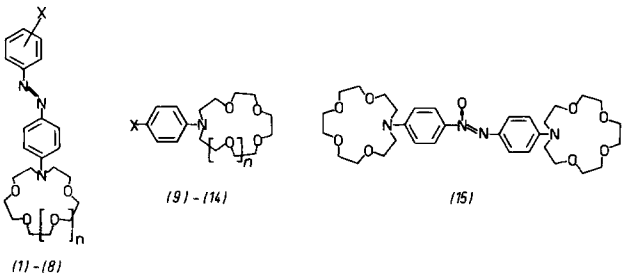
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[4] *P. Laszlo*, Angew. Chem. *90*, 271 (1978); Angew. Chem. Int. Ed. Engl. *17*, 254 (1978).
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[7] We have checked that line broadening due to chemical exchange between sites having different chemical shifts has a negligible effect under the conditions of this study.
[8] a) *S. N. Deming, S. S. Morgan*, Anal. Chem. *45*, 278A (1973); b) *D. Live, S. I. Chan*, J. Am. Chem. Soc. *98*, 3769 (1976).
[9] Standard deviations are 5.9 kJ mol^{-1} and 21 J mol^{-1} K^{-1} on the enthalpy and entropy of complexation respectively.
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Ion-Selective Crown Ether Dyes

By *J. Peter Dix* and *Fritz Vögtle*[*]

A molecular combination of dyes with crown ethers is desirable for a variety of reasons: one point of interest is the influence of selective complex formation with alkali or alkaline earth metal ions[1], made possible by crown ether structural units, on the absorption of the chromophore. Moreover, crown ether dyes should be suitable for detection of phase transfer of salts and for the study of ion transport through lipophilic media[2].

We have therefore incorporated crown ethers into dye molecules in such a manner that the chromophore is influenced *directly* on complexation with cations: the dimethylamino group in the azo dyes methyl orange, methyl red, *etc.* was

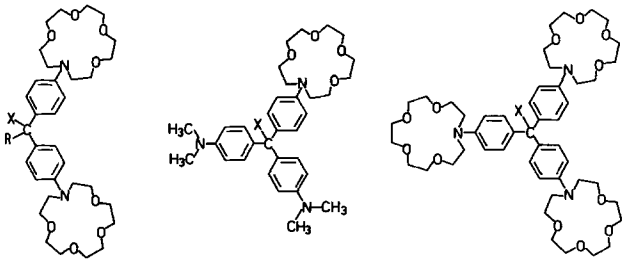


formally replaced by a "crown ether amine" group. In order to synthesize compounds *(1)* to *(8)*, we first prepared the *N*-phenyl crown ether amines *(9)* to *(11)* of various ring widths and transformed them by azo coupling into *(1)* to *(8)*.

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Compound *(9)* was converted into the *p*-nitrosodimethylaniline-analogous crown ether *(12)*; reduction of *(12)* gave *(13)* and *(15)*; Vilsmeyer reaction of *(9)* afforded the aldehyde *(14)* (see Table 1 for data).

In order to compare various dye systems, the dimethylamino groups of the diphenylmethane dye Michler's hydrol blue and the triphenylmethane dyes malachite green and crystal violet were successively replaced by "crown ether amine



(16)-(18) *(19)* *(20)*

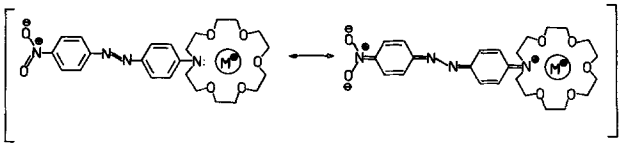
groups". Synthesis of compounds *(16)*—*(20)* was achieved by Friedel-Crafts reaction of *(9)* with carbonyl compounds (data for the isolated leuco compounds X=H, see Table 1).

Table 1. Data of the synthesized crown ether dyes. Correct elemental analyses or high resolution mass spectra and uniform thin layer chromatograms were obtained for all the compounds listed.

Cpd.	X	R	*n*	M.p. [°C]	λ_{max} [nm] [a]	Complex with (m.p. [°C])
(1)	*p*-SO_3Na		1	138—145	418	
(2)	*o*-COONa		1	139—149		
(3)	*p*-NO_2		1	132—134	474	LiClO (254—256) NaSCN (168—171) KSCN [b] (145)
(4)	*p*-NO_2		2	111—116	474 [c] 477	
(5)	*p*-NO_2		3	95—97	477	
(6)	*m*-NO_2		1	110	435.5	
(7)	*p*-COOEt		1	115	440	
(8)	H		1	[b]	413	
(9)	H		1	44—45		$NaClO_4$ (153—156)
(10)	H		2	30—35		KSCN (137—142)
(11)	H		3	oil [b]		
(12)	*p*-NO		1	127	420	NaSCN (160)
(13)	*p*-NH_2		1	46		
(14)	*p*-CHO		1	80		
(15)				145—151	421.5	
(16a)	H	H	1	80—85		
(16b)	C_2O_4H	H	1	—	610	
(17a)	H	C_6H_5	1	117—121		
(17b)	$C_6HCl_4O_2$	C_6H_5	1		622 426.5	
(18a)	H	[d]	1	oil		
(18b)	Cl	[d]	1		588.0	
(19a)	H		1	125—127		
(19b)	$C_6HCl_4O_2$		1		587.0	
(20a)	H		1	oil		
(20b)	$C_6HCl_4O_2$		1		489.5 470	
(21)						

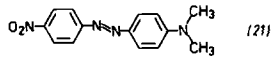
[a] In acetonitrile. [b] Although detected unequivocally (NMR, MS) this compound could not be obtained absolutely pure. [c] In methanol. [d] R = *p*-$(CH_3)_2N$—C_6H_4-.

The selective inclusion of alkali metal, alkaline earth metal, ammonium, and heavy metal ions, as well as H_3O^+ in such crown ether dyes should exert a selective influence on the chromophore including the nitrogen of the crown ether amine because the lone pair contributing to resonance will be affected to a greater or lesser extent by the positive charge of the guest ion, depending upon the nature of the ion concerned[3]:



(4a)·$M^{\oplus}$ *(4b)*·$M^{\oplus}$

As shown by the UV spectra of the *p*-nitrophenyl azo dyes *(3)*—*(5)*, considerable characteristic differences are observed for the various cations as compared with the only slightly ionically active "parent dye" *(21)* with a dimethylamino group (Table 2).



(21)

Table 2. Difference ($\Delta\lambda$) between the strongest absorption band of the crown ether dyes *(3)*—*(5)* and the reference substance *(21)* before and after addition of salt (in acetonitrile); concentrations of ligand, salt $\leq 1:10$. −: hypsochromic shift, +: bathochromic shift.

Added salt	Difference ($\Delta\lambda$) [nm] *(3)*	*(4)*	*(5)*	*(21)*
$LiClO_4$	−10	− 4	− 7	+1
LiI	− 9.5	− 3.5	− 7.5	
$NaClO_4$	− 8.5	− 10	− 5.5	
NaSCN			− 4.5	
NaI	− 8.5	− 7	− 5	0
KI	0	− 20	− 5.5	+1
KSCN	− 1.5		− 5	
RbI	0	− 6.5	− 7	
CsI	0	− 4.5	−11	
MgI_2	− 1.5	− 13	− 3	[4]
$Ca(SCN)_2$	− 7.5	− 26	−13	+1
NaI_2	[a]	−120		
$Ba(SCN)_2$	[a]	−117.5	− 7	+1
$CuCl_2$	−19		− 2	
$(CH_3)_3CNH_3SCN$		− 2		
NH_4SCN		− 8		
$ZnCl_2$	+ 0.5			

[a] −2 to −10; very dependent upon salt concentration.

On variation of the ring width, the expected selective complexation occurs with added alkali and alkaline earth metal ions, which led to widely varying shifts or changes in intensity of the absorption bands. The alkali metal ion fitting into the crown ether cavity leads to the greatest hypsochromic shift: Li^+/Na^+ for *(3)*, K^+ for *(4)*, Cs^+ for *(5)*. As is also shown by Table 2, the change in the absorption bands is the greatest for the [18]crown dye *(4)* and Ba^{2+} ions ($\Delta\lambda \approx 120$ nm). Much smaller changes in absorption are observed for the smaller and larger crown ether amines *(3)* and *(5)*; neither significant wavelength shifts on addition of ions (*e.g.* $\Delta\lambda = +1$ nm for Ba^{2+}[4]) nor ion selectivity of light absorption are observed for the parent dye *(21)*.

Table 2 shows that the anions have very little effect on the absorption.

The appearance of the band at 357 nm on addition of Ba^{2+} salts to *(4)* could be due to the fact that this cation has such a drastic effect on the "lone" electron pair of the amino nitrogen, because its volume fits the crown ether cavity and because of its high charge density [cf. *(4a)*·$M^+ \leftrightarrow$ *(4b)*·M^+], that almost exclusively the nitro-substituted azobenzene acts as chromophore (λ_{max} 332 nm[3]).

The ability of the crown ether dyes to form stable complexes was also evidenced by the isolation of a number of crystalline alkali metal salt complexes (Table 1).

Since crown ether (or cryptand[5]) structural units can be incorporated into many other dye systems, novel quantitative data can be obtained on the selective modification of host molecules containing chromophores by guest particles in various media.

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CAS Registry numbers:
(1), 66769-43-5; *(2)*, 66769-42-4; *(3)*, 66750-14-9; *(3)*·NaSCN, 66758-65-4; Table 2, complexes with *(3)* (from top to bottom), 66758-50-7; 66758-48-3; 66758-47-2; 66758-45-0; 66758-44-9; 66758-64-3; 66758-62-1; 66758-61-0; 66770-06-7; 66758-60-9; 66758-58-5; 66758-57-4; 66758-55-2; 66758-54-1; *(4)*, 66750-29-6; Table 2, complexes with *(4)* (from top to bottom), 66750-21-8; 66750-19-4; 66750-18-3; 66750-16-1; 66750-15-0; 66750-32-1; 66750-31-0; 66750-30-9; 66769-28-6; 66750-28-5; 66769-26-4; 66922-21-2; 66922-20-1; *(5)*, 66750-27-4; Table 2, complexes with *(5)* (from top to bottom), 66750-26-3; 66750-24-1; 66750-23-0; 66769-39-9; 66769-41-3; 66750-06-9; 66769-38-8; 66750-04-7; 66750-03-6; 66750-02-5; 66769-36-6; 66769-34-4; 66750-01-4; *(6)*, 66750-13-8; *(7)*, 66750-12-7; *(8)*, 66750-11-6; *(9)*, 66750-10-5; *(9)*·$NaClO_4$, 66750-00-3; *(10)*, 66750-09-2; *(10)*·KSCN, 66769-32-2; *(11)*, 66750-08-1; *(12)*, 66750-07-0; *(12)*·NaSCN, 66769-30-0; *(13)*, 66750-05-8; *(14)*, 66749-96-0; *(15)* 66769-99-1; *(16a)*, 66749-95-9; *(16b)*, 66749-94-8; *(17a)*, 66749-93-7; *(17b)*, 66769-40-2; *(18a)*, 66749-92-6; *(18b)*, 66749-91-5; *(19a)*, 66749-90-4; *(19b)*, 66749-98-2; *(20a)*, 66749-97-1; *(20b)*, 66769-24-2; *(21)*, 2491-74-9

[1] Review: *F. Vögtle, E. Weber*, Kontakte (Merck) *1977*, (1), 11; *1977* (2), 16; *1977*, (3), 34.
[2] Reviews: *W. Burgermeister, R. Winkler-Oswatitsch*, Top. Curr. Chem. *69*, 91 (1977); *Yu. A. Ovchinnikov, V. T. Ivanow, A. M. Shkrob:* Membrane-active Complexones. Elsevier, Amsterdam 1974; *C. J. Duncan:* Calcium in Biological Systems. Cambridge University Press 1976.
[3] *J. Griffiths:* Colour and Constitution of Organic Molecules. Academic Press, London 1976.
[4] MgI_2 is an exception, inducing a hypsochromic shift.
[5] In addition to a shift of equilibrium in favor of the complex, cryptand systems should give rise to greatest cation selectivity.

Carbonylation of Transition-Metal Carbyne Complexes, a New Method for the Synthesis of Metal-Substituted Ketenes[**]

By *Fritz R. Kreissl, Wolfgang Uedelhoven*, and *Karl Eberl*[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

Only a few examples of reactions of carbon monoxide with carbene- and carbyne-complexes have so far been reported in the literature. One example is the reaction of a mixture of methoxy(phenyl)carbenepentacarbonylchromium and 1-vinyl-2-pyrrolidone with CO at 150 atm and 80 °C to give a highly substituted vinyl ketone; methoxy(phenyl)ketene was postulated as intermediate[1].

If, however, *p*-tolylcarbynecarbonyl(cyclopentadienyl)trimethylphosphane complexes of molybdenum and tungsten[2] are allowed to react with CO, carbonylation at the carbyne carbon already takes place at normal pressure and −30 °C:

$$C_5H_5(CO)[P(CH_3)_3]M{\equiv}C{-}C_6H_4CH_3 + 2\,CO \longrightarrow$$

(1)

$$C_5H_5(CO)_2[P(CH_3)_3]M{-}C(=C{=}O){-}C_6H_4CH_3$$

(2)

(a): M = Mo, *(b)*: M = W

The products *(2a)* and *(2b)*[3] crystallize as bright-yellow needles and are readily soluble in acetone or dichloromethane, but insoluble in ether and pentane. On the basis of secondary reactions[4] at the ketene function the two longwave νCO bands of the new compounds (in CH_2Cl_2: *(2a)* 1943 s, 1855 vs; *(2b)* 1930 s, 1836 vs cm^{-1}) can be assigned to the carbonyl ligand, and the very strong bands at 2029 and 2022 cm^{-1} to the η^1-ketenyl ligand.

The ^{1}H-NMR spectrum (CD_2Cl_2) shows for *(2b)* four signals of relative intensity 4:5:3:9, which correspond to the aryl- (δ = 7.14), cyclopentadienyl- (δ = 5.35), methyl- (δ = 2.33) and *P*-methyl protons (δ = 1.78). The signals at δ = 5.35 and 1.78 appear as doublets owing to ^{31}P-^{1}H coupling (J = 2.2 and 9.2 Hz).—In the $^{31}P\{^1H\}$-NMR spectrum[5] (CD_2Cl_2, rel. to H_3PO_4 ext.) a singlet accompanied by two satellites is observed at δ = −14.99 with $^1J(^{183}W$-$^{31}P)$ = 174.0 Hz.—Valuable information on the structure is provided by the $^{13}C\{^1H\}$-NMR spectrum[5] (CD_2Cl_2, −40 °C, δ-value rel. to CD_2Cl_2 = 54.2 ppm; ^{31}P-^{13}C coupling constants in Hz): W—CO (224.13; 17.1), CO-ketene (156.43), C_6H_4 (137.34, 131.19, 129.14), C_5H_5 (90.95), CH_3 (20.93), PCH_3 (19.63; 34.2), C-ketene (−15.27; 7.3). The appearance of only one signal for both metalcarbonyl C-atoms affords proof of the *trans* orientation of the two CO-ligands, and thus also of the phosphane- and the ketenyl-ligand. The last signal, for the terminal ketene carbon with δ = −15.27, indicates an extraordinarily large shielding for sp^2-hybridized atoms[6].

Experimental

All operations should be carried out in dry (Na, P_4O_{10}) and N_2-saturated solvents.—*(2a)*: A solution of 0.37 g (3 mmol) *(1a)*[2] in 30 ml ether is treated at −30 °C with CO at a pressure of 1 at. The originally dark-red solution slowly decolorizes and a bright-yellow precipitate separates out. After *ca.* 5 h the crude product is decanted off and washed twice with 20 ml each of ether and pentane. Reprecipitation from CH_2Cl_2/ether/pentane affords fine yellow crystals; yield 0.29 g (69 %).—*(2b)*: A solution of 0.46 g (1 mmol) *(1b)*[2] in 30 ml ether is treated with CO and worked-up analogously to *(2a)*. Yellow crystals; yield 0.44 g (86 %).

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CAS Registry numbers:
(1a), 68129-63-5; *(1b)*, 68129-64-6; *(2a)*, 68129-65-7; *(2c)*, 68129-61-3; ^{13}C, 14762-74-4

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[3] The corresponding chromium compound as well as analogous methyl-phenyl-, mesityl, ferrocenyl- and triphenylsilyl-derivatives have also been synthesized and characterized.
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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

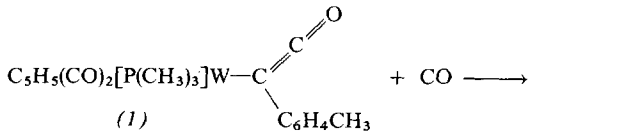
Deoxygenation—A Novel Reaction Path of Transition Metal-Substituted Ketenes[**]

By *Fritz R. Kreissl, Karl Eberl,* and *Wolfgang Uedelhoven*[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

Reduction, photolysis, and thermolysis of ketenes proceed almost exclusively with addition at the C=C- or C=O bond or with cleavage of the C=C double bond. The reduction of diphenylketene with triethyl phosphite leads to a 2:1 adduct, which on pyrolysis undergoes cleavage at the C=O double bond with formation of diphenylacetylene[1].

Transition metal-substituted ketenes[2] such as *(1)*, however, react with carbon monoxide cleanly to give the corresponding acetylene, also with cleavage of the C=O double bond.



$C_5H_5(CO)_2[P(CH_3)_3]W-C(=C=O)-C_6H_4CH_3$ + CO ⟶

(1)

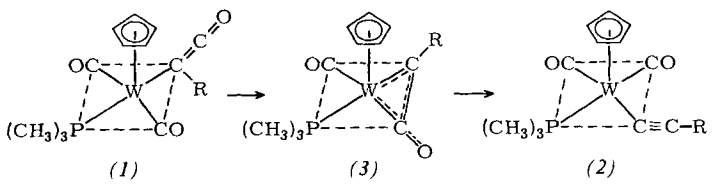
$C_5H_5(CO)_2[P(CH_3)_3]W-C\equiv C-C_6H_4CH_3 + CO_2$

(2)

The product *(2)* can be isolated as yellow diamagnetic crystals[3] which are readily soluble in dichloromethane and acetone. The composition and structure of the new complex were confirmed by elemental analysis and by its mass spectrum and IR and NMR spectra.

The IR spectrum (KBr; cm^{-1}) shows one band in the carbonyl region for the C≡C stretching vibration (2048 m) and two for the CO ligands (1935 vs, 1840 vs), the intensity pattern being consistent with a *cis* arrangement of the two CO groups[4].—The ^{1}H-NMR spectrum (CD_3COCD_3) contains four signals of relative intensity 4:5:3:9 which are assigned to the aryl- (δ = 7.21), cyclopentadienyl- (δ = 5.74), methyl- (δ = 2.37) and *P*-methyl-protons (δ = 1.89). The signals at δ = 5.74 and 1.89 occur as doublets (J = 0.6 and 9.8 Hz) as a result of ^{31}P-^{1}H coupling.—The ^{13}C{^{1}H}-NMR spectrum (CD_3COCD_3, δ-values rel. to CD_3COCD_3 = 206.5 ppm; ^{183}W-^{13}C- and ^{31}P-^{13}C-coupling constants in Hz) contains eleven signals: W—CO 247.70 (139.7; 23.5), 232.56 (142.7; 5.9); C_6H_4 135.47, 131.31 (—; 2.9), 129.88, 126.89 (—; 2.9); W—C≡*C* 127.41 (—; 2.9); W—*C*≡C 96.34 (97.1; 41.2); C_5H_5 91.92; CH_3 21.73; PCH_3 19.49 (—; 36.8). We assign the carbonyl resonance at δ = 247.70 to the CO group *trans* to the acetylene residue[2,5].—In the ^{31}P{^{1}H}-NMR spectrum (CD_2Cl_2, rel. to H_3PO_4 ext.) a singlet accompanied by satellites appears at δ = −7.83 with $^1J(^{183}W-^{31}P)$ = 225.8 Hz.

The reorientation of the original η^1-ketenyl ligands and the change in configuration of the two carbonyl ligands from *trans* to *cis* during the conversion of *(1)* into *(2)* would suggest that the reaction probably proceeds *via* the η^2-ketenyl intermediate *(3)*[6], but, does not rule out a 1,2-shift of the *p*-tolyl substituents. In contrast to *(1)*, diphenylketene does not react to give an analogous acetylene derivative under similar conditions.



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

R = *p*-$C_6H_4CH_3$

Anionic and neutral complexes analogous to *(2)* have already been prepared by reaction of alkali-metal acetylides with hexacarbonyltungsten and tricarbonyl(chloro)cyclopentadienylmolybdenum respectively[7].

Experimental

All operations should be carried out in dry (Na/K, P_4O_{10}) and N_2-saturated solvents. A solution of 2.5 g (5 mmol) *(1)*[2] in 40 ml dichloromethane is transferred to a hand autoclave at room temperature. After introduction of CO at 60 atm, the autoclave is allowed to stand for 24 h at 60 °C. On release of pressure the yellow-brown solution is filtered and chromatographed on silica gel at −30 °C with ether/dichloromethane (1:1). Recrystallization from acetone and drying *in vacuo* affords pure *(2)*; yield 2.1 g (80 %).

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CAS Registry numbers:
(1), 68129-61-3; *(2)*, 68129-62-4; ^{13}C, 14762-74-4

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Oxygen Evolution from Water *via* Redox Catalysis[**]

By *John Kiwi* and *Michael Grätzel*[*]

The production of chemical fuel from light *via* the photoredox reaction

$$A + D \underset{\Delta}{\overset{h\nu}{\rightleftharpoons}} A^- + D^+ \qquad (1)$$

encounters two major obstacles, one of which is related to the reversibility of reaction (1), leading to thermal degradation of photon energy. This problem may be overcome by using suitable molecular devices such as micellar or membrane assemblies as a reaction medium[1,2] to suppress or considably retard the back reaction. Once A^- and D^+ have been stabilized the task remains to convert their chemical potential into useful products. For example, A and D may be selected such that

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in aqueous solution oxygen and hydrogen evolution becomes thermodynamically feasible.

$$2A^- + H_2O \rightarrow 2A + 2OH^- + H_2 \quad (2)$$
$$4D^+ + H_2O \rightarrow 4D + 4H^+ + O_2 \quad (3)$$

Reactions (2) and (3), which do not usually occur spontaneously, can be accelerated by suitable redox catalysts. These catalysts also prevent other destructive pathways of A^- and D^+ deactivation. Recently[3–5], this principle was successfully applied to hydrogen evolution by process (2).

The present paper reports the first evidence that the production of oxygen *via* reaction (3) may also be mediated by a redox catalyst. The investigations were conducted with the Ce^{4+}/Ce^{3+} couple as D^+/D system. Ce^{4+} is relatively stable in aqueous H_2SO_4 although from its redox potential ($E^0 = 1.44$ V) it should spontaneously liberate oxygen from water. The Ce^{3+} produced can regenerate Ce^{4+} photochemically, with simultaneous production of H_2[6]. Thus the cycle of light-induced water decomposition is closed.

Cerium(IV) sulfate (Merck pro analysis), PtO_2 (Adams catalyst, Fluka puriss.), and IrO_2 (Sigma) were used as supplied. Deionized water was distilled from a MnO_4^- solution, and subsequently twice from a quartz still. UV spectra were recorded on a Cary-219 spectrophotometer. An oxygen electrode (O_2 meter Portomatic model 376, Instrumentation Laboratory) was employed to monitor the evolution of oxygen.

Experiments were carried out with a three-neck flat-bottom flask. Two necks accepted the oxygen electrode and the glass tube for deoxygenation, while the third was plugged with a gas-impermeable septum permitting samples of the solution to be taken for optical analysis. Thus during the procedure of stirring with the catalyst the Ce^{4+} concentration could be checked continuously by absorbance measurements; an extinction coefficient[7] of 5.92×10^3 l mol^{-1} cm^{-1} was used in the calculations.

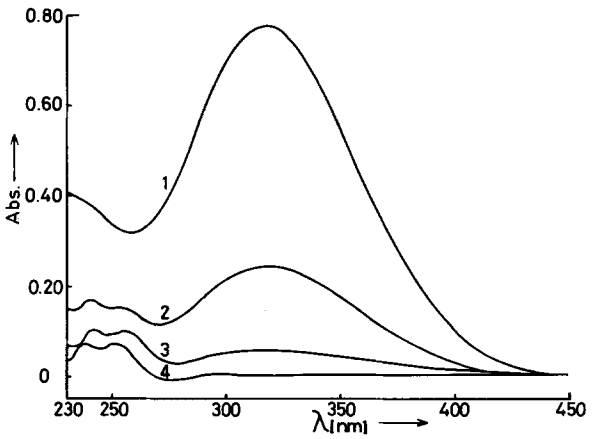


Fig. 1. Temporal behavior of the absorption spectra of solutions of $Ce(SO_4)_2$ (2.7×10^{-3} mol/l) in 1 N H_2SO_4 in the presence of PtO_2 (32 mg/100 ml H_2O). 1, after zero time; 2, after 2 h; 3, after 8 h; 4, after 16 h.

Figure 1 shows the spectral changes observed when a solution of $Ce(SO_4)_2$ is stirred with Adams catalyst. The Ce^{4+} absorption spectrum present at zero time diminishes within a few hours, and a new absorption band appears around 250 nm which is characteristic[8] of Ce^{3+} ions. Figure 2 shows that the conversion of Ce^{4+} into Ce^{3+} is associated with the formation of oxygen from water. In fact, by taking into account the amount of oxygen which escapes from the solution into the gas phase, it was found that for every molecule of oxygen produced four Ce^{4+} ions are reduced to Ce^{3+}.

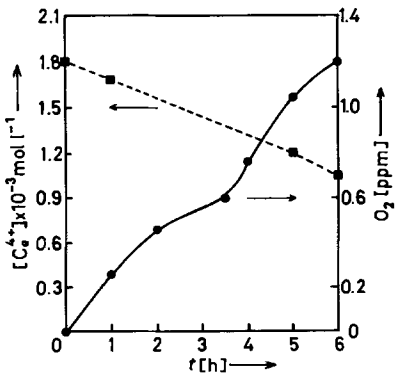


Fig. 2. Evolution of oxygen and decrease of Ce^{4+} concentration in 1 N H_2SO_4 in the presence of PtO_2 (32 mg/100 ml H_2O).

For example, in a typical experiment (Fig. 2) the rate of oxygen evolution was found to be 3×10^{-5} mol l^{-1} h^{-1} while that of Ce^{4+} reduction was 1.2×10^{-4} mol l^{-1} h^{-1}. Hence, water oxidation

$$4Ce^{4+} + 2H_2O \rightarrow 4Ce^{3+} + 4H^+ + O_2 \quad (3a)$$

must occur quantitatively in the presence of the redox catalyst. Blank experiments carried out with solutions containing no redox catalyst showed only a 10 % decrease in Ce^{4+} concentration over 24 h. No oxygen evolution could be detected under these conditions.

The initial rate of Ce^{4+} reduction or O_2 evolution was found to increase linearly with Ce^{4+} concentration. It is also a function of the amount of catalyst present and the rate of stirring, *i.e.* the efficiency of contact between the catalyst and the solution.

Further studies showed that the reduction of tris(2,2'-bipyridine)ruthenium(III) by water according to

$$4Ru(bpy)_3^{3+} + 2H_2O \rightarrow 4Ru(bpy)_3^{2+} + 4H^+ + O_2 \quad (3b)$$

can also be promoted by redox catalysts such as PtO_2 or IrO_2. Thus, reaction (3b) occurs within 3 h in aqueous sulfuric acid solution of pH = 1 in the presence of PtO_2. Under these conditions, $Ru(bpy)_3^{3+}$ is practically stable over the same period[9] in catalyst free solution.

The latter result is particularly important since $Ru(bpy)_3^{2+}$ can be reconverted in a photoinduced redox reaction into $Ru(bpy)_3^{3+}$ with evolution of hydrogen[4, 5]. Hence, the cyclic production of H_2 and O_2 from water by illumination appears to be feasible in such a system.

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CAS Registry numbers:
O_2, 7782-44-7; H_2O, 7732-19-5; $Ce(SO_4)_2$, 13590-82-4

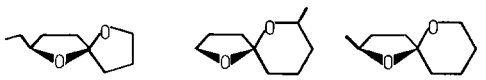
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Methyl-1,6-dioxaspiro[4.5]decanes as Odors of *Paravespula vulgaris* (L.)[**]

By *Wittko Francke*, *Gerd Hindorf*, and *Wolfgang Reith*[*]

In contrast to other social insects, no volatile components have yet been identified from the common wasp *P. vulgaris*[1].

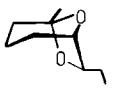
After the identification of 2-ethyl-1,6-dioxaspiro[4.5]nonane (chalcogran) *(1)*[2] as the principal aggregation pheromone of *Pityogenes chalcographus* L., we have now studied the mass-spectrometric fragmentation of volatile spiroketals[3] and found (GLC-MS coupling[4]) spiroketals to be present in the pentane extracts of the abdomina of *P. vulgaris* workers.



(1)

(2)

(3)



(4)



(5)

The main component and a trace substance proved to be, respectively, (*Z*)- and (*E*)-7-methyl-1,6-dioxaspiro[4.5]decane *(2)*[5], while two minor components were identified as equal amounts of (*Z*)- and (*E*)-2-methyl-1,6-dioxaspiro[4.5]decane *(3)*[6], along with traces of 2-nonanone.

The racemic compounds *(2)* and *(3)* were prepared from γ-butyrolactone and δ-caprolactone, and γ-valerolactone and δ-valerolactone, respectively, according to the procedure of *Erdmann* and *Ström*[7]. The synthetic substances purified by preparative GLC showed the same mass spectra and had similar retention times on GLC as the natural products, the chirality of which have not yet been clarified.

Remarkably, the new spiroketals *(2)* and *(3)* show an unbranched dihydroxynonanone skeleton, as do chalcogran *(1)*, 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (brevicomin) *(4)*[8], and 1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane *(5)*[9]. *(4)* is an attractant, and *(5)* is a compound occurring specifically in attacked spruce. Genetic relations cannot be excluded.

Preliminary bioassays showed that the new compounds might serve as repellents or aggression inhibitors, which could protect the individuals from attack by its fellow wasps. Dead extracted wasps hanging 12 cm in front of the entrance hole of an earth nest frequented by 40 individuals per minute were attacked within two minutes and then at intervals of 30—60 s. In contrast, extracted wasps previously treated with 0.1 mg of the spiroketals mixed in the naturally occurring proportions or freshly killed ones were only attacked after 8—10 min, the intervals between further attacks being much longer than before. Application of 0.1 mg of the spiroketal mixture to heavily frequented dummies inhibited any attack for 8—12 min. Each series of assays was repeated twelve times.

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(*Z*)-*(2)*, 68108-89-4; (*E*)-*(2)*, 68108-90-7; (*Z*)-*(3)*, 68108-91-8; (*E*)-*(3)*, 68108-92-9; γ-butyrolactone, 616-45-5; δ-caprolactone, 823-22-3; γ-valerolactone, 108-29-2; δ-valerolactone, 542-28-9

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

[1] *D. H. Calam*, Nature *221*, 856 (1969).
[2] *W. Francke, V. Heemann, B. Gerken, J. A. A. Renwick, J. P. Vité*, Naturwissenschaften *64*, 590 (1977).
[3] *W. Reith*, Diplomarbeit, Universität Hamburg 1978.
[4] Varian MAT 111, 50 m capillary 0.25 mm i.d.; Marlophen 87; 323—413 K; 2 K/min; 1 bar He.
[5] a) MS: *m/e* 87 (100%); 84 (81); 97=43 (23); 112=86 (18); 55 (13); 56 (11); 41 (10); 115=85=69=42 (8); 57 (7); 73=45 (5); 72=71=39 (4); 156 [$M^{\oplus}$]=70 (3); 126 (2); 141=128 (1); b) *J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, J. E. Rush*, J. Am. Chem. Soc. *90*, 509 (1968); the unsubstituted ring serves as reference plane.
[6] MS: *m/e* 101 (100%); 98=83 (40); 100 (33); 55 (28); 56=43 (20); 41 (17); 111=85 (12); 112 (11); 57 (10); 59 (9); 70=39 (6); 156 [$M^{\oplus}$]=128 (5); 141=71 (4); 69 (3); 67 (2).
[7] *H. Erdmann*, Justus Liebigs Ann. Chem. *228*, 176 (1885); *T. Ström*, J. Prakt. Chem. *48*, 209 (1893).
[8] *R. M. Silverstein, R. G. Brownlee, T. E. Bellas, D. L. Wood, L. E. Browne*, Science *159*, 889 (1968).
[9] *V. Heemann, W. Francke*, Naturwissenschaften *63*, 344 (1976).

Catalytic Carbon-Carbon Bond Formation with Carbene Intermediates

By *Gisela Henrici-Olivé* and *Salvador Olivé*[*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

We wish to report the transformation of methylamine (C_1) into acetonitrile (C_2), and on the mechanism of this process. Methylamine is a low cost, coal based, industrial chemical, obtained by alkylation of ammonia with methanol:

$$C \xrightarrow{\text{Oxygen}} CO \xrightarrow{\text{Hydrogen}} CH_3OH \xrightarrow{\text{Ammonia}} CH_3NH_2$$

When methylamine is passed over a silica/molybdenum catalyst at 400–500 °C, at a flowrate of 0.8×10^{-3} mol/min, it decomposes almost quantitatively. Traces of acetonitrile are formed, together with large amounts of HCN and NH_3. However, the yield of CH_3CN is greatly increased, if hydrogen accompanies the amine. At a molar ratio of $H_2:CH_3NH_2$ of 12:1, 20—30% of the methylamine is converted into acetonitrile[1]. Some propionitrile (<1%) is also formed; non-nitrogen containing by-products are mainly methane, with minor amounts of higher hydrocarbons (C_2—C_4).

The catalyst is prepared by impregnating silica (particle size 0.2—0.5 mm, Merck) with a water-soluble molybdenum compound (*e.g.* $[NH_4]_6Mo_7O_{24}\cdot 4H_2O$); after drying, the catalyst is oxidized with oxygen (8 h, 500 °C), and subsequently reduced with ammonia (17 h, 500 °C). It has about 5×10^{-4} g/atom of Mo per gram of catalyst. Molybdenum can be replaced by other transition metals, although with decreasing activity, in the series Mo > W > Cr > Ru > Fe ≫ Co ≈ Ni. On silica alone, the methylamine is recovered essentially unchanged. If silica is replaced by alumina in the catalyst, a carbonaceous deposit covers the alumina; no acetonitrile is observed.

The formation of acetonitrile according to the overall equation (1) is thermodynamically favorable; the equilibrium constant at 500 °C is $K_p = 1.6 \times 10^6$ atm[2][2].

$$2\ CH_3NH_2 \overset{K_p}{\rightleftharpoons} CH_3CN + NH_3 + 2\ H_2 \qquad (1)$$

To elucidate the detailed mechanism of the reaction depicted in Eq. (1), we carried out the process using deuterium instead

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of hydrogen, all other conditions remaining the same. Mass spectroscopic analysis[3] of the major hydrocarbon by-product, methane, yielded a very useful piece of information. Two samples of the noncondensable part of the product stream were taken, 30 and 90 min after the onset of the catalytic process. The isotopic distribution in the methane is given in Table 1.

Table 1. Isotopic distribution in methane formed as by-product during the synthesis of acetonitrile from methylamine and D_2 (SiO_2/Mo catalyst; $D_2:CH_3NH_2 = 12:1$).

Component	Distribution [mol %]	
	$t = 30$ min	$t = 90$ min
CH_4	15.7	16.0
CH_3D	18.2	20.1
CH_2D_2	32.9	32.5
CHD_3	25.0	23.6
CD_4	8.2	7.8

Evidently the deuterium has taken part in the formation of the methane. The distribution does not depend on the reaction time, and there is a distinct maximum for CH_2D_2. The latter fact excludes the formation of the deuterated methanes by a metal-catalyzed H/D exchange of CH_4 with D_2. A mechanism involving a carbene intermediate is suggested for the methane formation, in order to account for the maximum in CH_2D_2.

Methylamine is assumed to add oxidatively to the metal [Eq. (2)]. Reductive elimination of ammonia then generates a carbene ligand (carbene formation by α-elimination of H from a methyl ligand is known for several transition metals[4]). Oxidative addition of deuterium leads to species A [Eq. (3)], from which the metal catalyst can be regenerated *via* reductive elimination of the main methane component, CH_2D_2. Alternatively, species A can, in a series of equilibria, lead to CHD_3 and CD_4, in decreasing concentration. (Hydrogenation of carbene ligands to the corresponding saturated hydrocarbons has been demonstrated recently by *Casey et al.*[5].)

$$CH_3NH_2 + M \longrightarrow CH_3\text{–}M\text{–}NH_2 \longrightarrow CH_2{=}M + NH_3 \qquad (2)$$

$$CH_2{=}M + D_2 \rightleftharpoons CH_2(D)\text{–}M\text{–}D \longrightarrow CH_2D_2 \qquad (3)$$

(A) $\rightleftharpoons$ $CHD{=}M\text{–}H$

$CHD{=}M$ (D) $\longrightarrow CHD_3$

$CD_2{=}M$ (D) $\longrightarrow CD_4$

(- HD, + D_2)

The formation of CH_4 and CH_3D takes place in corresponding equilibria, but with H_2 instead of D_2; the required hydrogen is continuously formed in the process, according to Eq. (1), and by the simultaneous thermal decomposition of methylamine to HCN:

$$CH_3NH_2 \longrightarrow HCN + 2\ H_2 \qquad (4)$$

We suggest the carbene complex formed by reaction (2) to be the key intermediate in the catalytic formation of acetonitrile from methylamine. This proposal is essentially inspired by the work of *E. O. Fischer et al.*[6], who reported the insertion of the carbene ligand of a chromium-carbene complex into the H—C bond of HCN, giving rise to a nitrile. Assuming an intermediate oxidative addition of HCN, we formulate for the present case:

$$H_2C{=}M + HCN \longrightarrow H_2C(H)\text{–}M(CN) \longrightarrow CH_3CN + M \qquad (5)$$

The evidence presented for a carbene ligand on a heterogeneous catalyst corroborates the reaction mechanism suggested previously by us for the Fischer-Tropsch synthesis[7].

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CAS Registry numbers:
Methylamine, 74-89-5; acetonitrile, 75-05-8

[1] Higher yields reported in a recent patent were erroneous, due to problems encountered in analysis: *S. Olivé, G. Henrici-Olivé*, US-Pat. 4058548 (1977), Monsanto Company.
[2] *S. R. Auvil*, Corporate Research Laboratories, Monsanto Company, St. Louis; personal communication.
[3] We thank Dr. *O. P. Tanner*, Physical Science Center, Monsanto Company, St. Louis, for carrying out the mass spectroscopic analyses.
[4] *L. S. Pu, A. Yamamoto*, J. Chem. Soc. Chem. Commun. *1974*, 9; *N. J. Cooper, M. L. H. Green, ibid. 1974*, 761; *M. L. H. Green*, Pure Appl. Chem. *50*, 27 (1978); *R. R. Schrock*, J. Am. Chem. Soc. 97, 6577 (1975).
[5] *C. P. Casey, S. M. Neuman*, J. Am. Chem. Soc. 99, 1651 (1977).
[6] *E. O. Fischer, S. Fontana, U. Schubert*, J. Organomet. Chem. *91*, C7 (1975).
[7] *G. Henrici-Olivé, S. Olivé*, Angew. Chem. *88*, 144 (1976); Angew. Chem. Int. Edit. Engl. *15*, 136 (1976); J. Mol. Catal. *3*, 443 (1977/78).

Heteronuclear Cobalt Clusters by Metal Exchange[**]

By *Harald Beurich* and *Heinrich Vahrenkamp*[*]

The synthesis of heterometallic clusters is even less predictable than that of clusters of a single metallic element. This aim has been achieved in various cases with concomitant cluster enlargement in a semi-systematic manner by "attachment" of additional metal atoms to existing clusters *via* addition or substitution reactions[1]. To our knowledge, specific incorporation of metal atoms by metal exchange has not previously been reported[2]; it has now been accomplished by an addition-elimination sequence.

We have repeatedly observed cobalt-containing, arsenic-bridged polynuclear complexes to undergo decomposition, with formation of an oligomeric, sparingly soluble product of approximate composition $[(CO)_3Co\text{—}AsMe_2]_x$ *(1)*[3], leading to the complexes containing one less metal atom [cf. reaction (A)[4a] and (B)[4b]]. Application of this reaction to the substituted methylidyne-tricobalt cluster *(2)* effects introduction of the heterometal atom in place of a cobalt atom. The addition step of this directed cluster synthesis consists in the attachment of the As—M unit to the $RCCo_3(CO)_9$ unit by tried and tested methods[4a,c]. The elimination step consists in the decomposition reaction (C). So far, we have prepared eleven new hetero-clusters *(3)* by this method (cf. Table 1).

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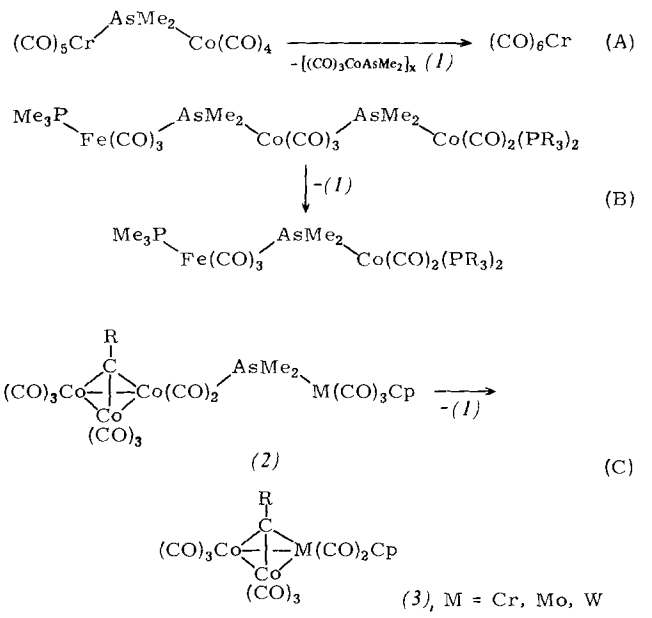


Table 1. Melting points and NMR data of the heteronuclear cobalt clusters *(3)*.

	R	M		^{1}H-NMR [b]	
			M.p. [°C]	δ(R)	δ(C_5H_5)
(3a)	H	Cr	129	12.91	4.96
(3b)	H	Mo	143	11.27	5.42
(3c)	H	W	147	11.79	5.46
(3d)	CH_3	Cr	155 [a]	3.94	4.91
(3e)	CH_3	Mo	200 [a]	3.73	5.35
(3f)	CH_3	W	205 [a]	3.84	5.41
(3g)	C_6H_5	Cr	137 [a]	7.22 (m)	4.68
(3h)	C_6H_5	Mo	165 [a]	7.21 (m)	5.22
(3i)	C_6H_5	W	173	7.16 (m)	5.34
(3j)	p-$C_6H_4CH_3$	Mo	151	7.06 (m), 2.36	5.23
(3k)	p-$C_6H_4CH_3$	W	169	7.02 (m), 2.39	5.33

[a] Decomposition. [b] In CCl_4, rel. to int. TMS; m = multiplet.

The green complexes *(3)*, which are air-stable as solids, can be readily identified on the basis of their simple NMR spectra. The well-populated IR spectra are similar in the CO region [*e.g. (3f)*: 2075 vw, 2066 m, 2035 sh, 2029 vs, 2010 s, 2000 vs, 1991 m, 1944 cm^{-1} m]. Confirmation was sought by determining the crystal and molecular structure of *(3h)*[5] (Fig. 1). The molecular parameters of *(3h)* correspond to those expected from reference substances[1b, 6].

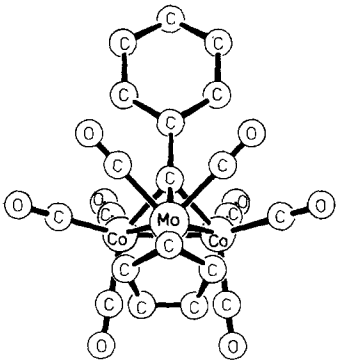


Fig. 1. Molecular structure of the hetero-cluster *(3h)*. Principal bond lengths: Co—Co = 248.3(1), Co—Mo = 267.7(1), Co—C = 193.3(5), Mo—C = 210.4(7) pm; bond angles: CoMoCo = 55.28(3), CoCoMo = 62.36(2), CoCMo = 83.0(2), CoCCo = 79.9(3)°.

Complexes *(3)* demonstrate that the chemistry of methylidyne-trimetal clusters, although so far examined thoroughly only for tricobalt compounds, can also be studied with other metals. Moreover, the incorporation of heterometal atoms in place of cobalt would appear to be a versatile synthetic procedure in view of the large number of known cobalt clusters. Preliminary results[7] support these expectations.

Experimental

$CH_3CCo_3(CO)_8$—$AsMe_2$—$Mo(CO)_3Cp$ *(2e)* (2.34 g, 3.1 mmol) is stirred in cyclohexane (50 ml) for 8 d at 40 °C. After filtration and concentration to a volume of 20 ml, the reaction solution is chromatographed on a silica gel column ($d = 3$, $l = 30$ cm) with hexane/benzene (4 : 1): a short first fraction of $CH_3CCo_3(CO)_9$ is followed by a green solution of *(3e)* which is evaporated to dryness *in vacuo*. Recrystallization from hexane (5 ml) affords *(3e)* (1.24 g, 75 %) as black crystals.

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CAS Registry numbers:
(2a), 68212-41-9; *(2b)*, 68185-29-5; *(2c)*, 68185-30-8; *(2d)*, 68212-40-8; *(2e)*, 68185-31-9; *(2f)*, 68185-32-0; *(2g)*, 68185-33-1; *(2h)*, 68185-34-2; *(2i)*, 68185-35-3; *(2j)*, 68185-36-4; *(2k)*, 68185-37-5; *(3a)*, 68185-38-6; *(3b)*, 68185-39-7; *(3c)*, 68185-40-0; *(3d)*, 68185-41-1; *(3e)*, 68185-42-2; *(3f)*, 68185-43-3; *(3g)*, 68185-44-4; *(3h)*, 68185-45-5; *(3i)*, 68185-46-6; *(3j)*, 68185-47-7; *(3k)*, 68185-48-8

[1] Cf. a) *H. Vahrenkamp*, Struct. Bonding (Berlin) *32*, 1 (1977); b) *G. Schmid*, Angew. Chem. *90*, 417 (1978); Angew. Chem. Int. Ed. Engl. *17*, 392 (1978); c) for very recent examples, see *M. R. Churchill, F. J. Hollander, J. R. Shapley, D. S. Foose*, J. Chem. Soc. Chem. Commun. *1978*, 534; *L. J. Farrugia, J. A. K. Howard, P. Mitrprachachon, J. L. Spencer, F. G. A. Stone, P. Woodward*, ibid. *1978*, 260.
[2] Cf. *M. H. Chisholm, M. W. Extine, R. L. Kelly, W. C. Mills, C. A. Murillo, L. A. Rankel, W. W. Reichert*, Inorg. Chem. *17*, 1673 (1978).
[3] *Y. L. Baay, A. G. MacDiarmid*, Inorg. Chem. *8*, 986 (1969).
[4] a) *W. Ehrl, H. Vahrenkamp*, Chem. Ber. *106*, 2550 (1973); b) *H. J. Langenbach, H. Vahrenkamp*, unpublished; c) *R. Müller, H. Vahrenkamp*, Chem. Ber. *110*, 3910 (1977).
[5] Orthorhombic, Pnma, $Z = 4$; $a = 1888.0(5)$, $b = 1246.2(4)$, $c = 905.6(2)$ pm; 1703 reflections, $R = 0.036$.
[6] *R. J. Dellaca, B. R. Penfold*, Inorg. Chem. *11*, 1855 (1972); *P. W. Sutton, L. F. Dahl*, J. Am. Chem. Soc. *89*, 261 (1967).
[7] *F. Richter, H. Vahrenkamp*, Angew. Chem. *90*, 916 (1978); Angew. Chem. Int. Ed. Engl. *17*, 864 (1978).

An Entry to Chiral Clusters[**]

By *Felix Richter* and *Heinrich Vahrenkamp*[*]

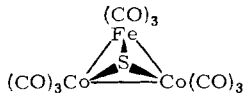
No optically active metal complex[1] is known whose chirality arises from differences between the metal atoms. On the basis of an analogy proposed between clusters and metal surfaces[2], such a polynuclear complex could serve as a model compound for asymmetric catalysis. We now report the first μ_3-bridged trinuclear complexes whose tetrahedral skeleton is made up of four different entities and should therefore impart chirality to the molecule.

The readily accessible[3] $FeCo_2$ cluster *(1)* and its conventionally prepared[4] substitution products *(2)* are transformed into the new clusters *(3)* containing three different metal atoms by our newly discovered[5] method of eliminating $[(CO)_3Co—AsMe_2]_x$. The complexes *(3)* are dark red to black in the solid state and red in solution, and exhibit a large number of absorption bands in the CO region of their

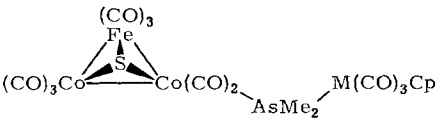
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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We are grateful to Dr. *P. Merbach*, Universität Erlangen-Nürnberg, for the mass spectrum.

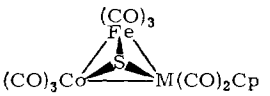
IR spectra [*e.g. (3b)*: 2080 s, 2038 vs, 2035 sh, 2020 s, 1998 s, 1985 m, 1895 cm^{-1} vw]. Their compositions were confirmed by the EI mass spectrum of *(3a)*. They differ from the sole known clusters with three different metal atoms[6] in their facile synthesis and the absence of any symmetry element in the molecule.



(1)



(2), M = Cr, Mo, W

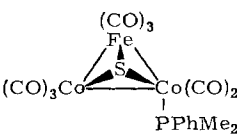


(3)

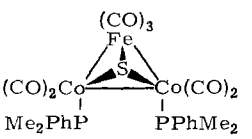
	M	M.p. [°C]	$\delta(C_5H_5)$ [a]
(3a)	Cr	102	4.20
(3b)	Mo	93	4.35
(3c)	W	112	4.33

[a] In benzene, rel. to int. TMS.

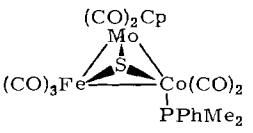
The chirality of the clusters *(3)* can be demonstrated by ^{1}H-NMR spectroscopy of suitable phosphane derivatives with diastereotopic *P*-substituents. The same applies to the starting complex *(1)* which likewise becomes chiral on CO/PR_2R' exchange. With this purpose in mind, the dimethyl(phenyl)-phosphane complexes *(4a)*, *(4b)*, *(5a)*, and *(5b)* were prepared and their structures assigned on the basis of the finding that ligand exchange in *(1)* first takes place at the two cobalt atoms[7] and that the ease of substitution decreases with decreasing number of CO groups attached to a metal atom. In all four substituted clusters the phosphane ligands are attached to asymmetric metal atoms; a *meso* form is present in the case of *(4b)*[8].



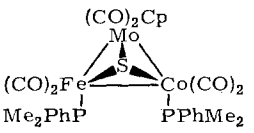
(4a)



(4b)



(5a)



(5b)

Table 1 and Figure 1 list the relevant NMR information; in all four cases the spectra have the expected appearance. It is informative to compare the disubstituted clusters: two identical centers of asymmetry are seen for *(4b)*, and two different ones for *(5b)*.

Table 1. ^{1}H-NMR data for the *P*-methyl groups of the clusters *(4)* and *(5)* (in benzene, rel. to int. TMS).

	$\delta(PCH_3)$	$^2J_{PH}$ [Hz]
(4a)	1.10, 1.17	10.0, 10.0
(4b)	1.25, 1.28	8.8, 8.8
(5a)	1.35, 1.37	9.0, 9.2
(5b)	1.44, 1.46, 1.48, 1.53	9.0, 9.1, 8.5, 8.8

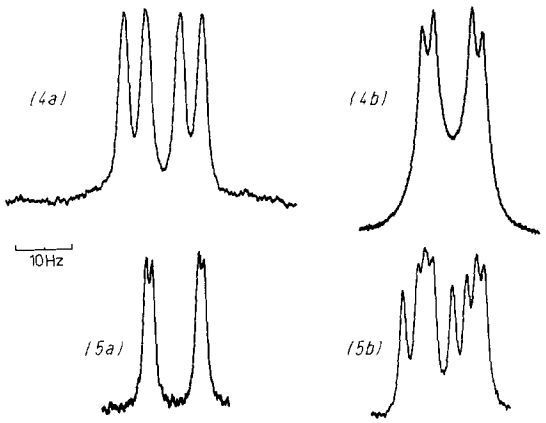


Fig. 1. ^{1}H-NMR spectra of the complexes *(4)* and *(5)* in the *P*-methyl region at 60 MHz.

Our results show that the synthesis of chiral clusters is now feasible. Attempts to introduce other metals into *(1)* and to resolve the enantiomers of the pure clusters are currently in progress.

Experimental

Compound *(2b)* (M = Mo) (0.50 g, 0.64 mmol) is heated in cyclohexane (50 ml) with stirring for 2 d at 70 °C. The reaction mixture is then chromatographed on a silica gel column ($d = 3$, $l = 70$ cm) with benzene/hexane (1 : 2), the second, red, fraction being collected. After evaporation to dryness, recrystallization from hexane (20 ml) affords *(3b)* (0.24 g, 70 %) as black-red crystals.

Compounds *(3a)* and *(3c)* were obtained similarly. The preparation of the phosphane-substituted clusters was accomplished in a manner resembling known procedures[7].

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CAS Registry numbers:
(2a), 68185-53-5; *(2b)*, 68185-54-6; *(2c)*, 68212-39-5; *(3a)*, 68212-38-4; *(3b)*, 68185-55-7; *(3c)*, 68185-56-8; *(4a)*, 68185-57-9; *(4b)*, 68185-58-0; *(5a)*, 68185-59-1; *(5b)*, 68185-60-4

[1] Cf. *H. Brunner*, Angew. Chem. *83*, 274 (1971); Angew. Chem. Int. Ed. Engl. *10*, 249 (1971).
[2] *H. Vahrenkamp*, Struct. Bonding (Berlin) *32*, 1 (1977); *E. L. Muetterties*, Angew. Chem. *90*, 577 (1978); Angew. Chem. Int. Ed. Engl. *17*, 545 (1978).
[3] *L. Markó*, personal communication; *S. A. Khattab*, *L. Markó*, *G. Bor*, *B. Markó*, J. Organomet. Chem. *1*, 373 (1964).
[4] *W. Ehrl*, *H. Vahrenkamp*, Chem. Ber. *106*, 2550 (1973); *R. Müller*, *H. Vahrenkamp*, *ibid. 110*, 3910 (1977).
[5] *H. Beurich*, *H. Vahrenkamp*, Angew. Chem. *90*, 915 (1978); Angew. Chem. Int. Ed. Engl. *17*, 863 (1978).
[6] *G. L. Geoffroy*, *W. L. Gladfelter*, J. Am. Chem. Soc. *99*, 7565 (1977).
[7] *S. Aime*, *L. Milone*, *R. Rossetti*, *P. L. Stanghellini*, Inorg. Chim. Acta *25*, 103 (1977).
[8] Complexes *(4)* and *(5)* were characterized by elemental analysis and spectra. The NMR data (Table 1) were determined by measurement at two different frequencies.

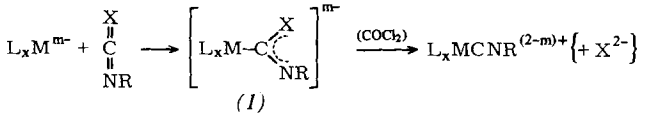
Systematic Formation of Metal Complexes Containing Isocyanide Bridging Ligands: $[\eta^5\text{-}C_5H_5Fe(CNC_6H_5)(\mu\text{-}CNC_6H_5)]_2$ [**]

By *Wolf Peter Fehlhammer, Andreas Mayr,* and *Götz Christian* [*]

Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

Metal complexes containing bridging isocyanide ligands are currently under investigation with regard to their catalytic activity[1], such as has recently been demonstrated for the nickel cluster $Ni_4(CNtBu)_7$[1a]. Most of these complexes have been obtained by reactions of carbonyl bridged metal complexes, which usually proceed in low yield affording mixtures of products.

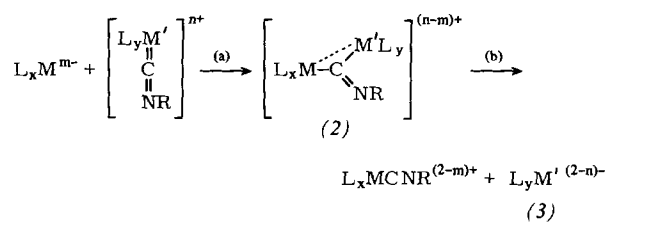
An essentially more effective preparation of μ-isocyanide complexes could be developed on the basis of our *isocyanide syntheses within a complex* from supernucleophilic metal bases and heteroallenes[2]. We had formulated the primary products of these reactions as adducts of type *(1)* which undergo elimination of X^{2-} either spontaneously or in the presence of Lewis acids (*e.g.* phosgene):



(1)

L_xM^{m-} = *e.g.* $Cr(CO)_5^{2-}$; X = NR, O, S

Formal replacement of the 6-electron heteroatoms X by 16-electron metal complex fragments L_yM' leads to an analogous scheme with the dinuclear isocyanide-bridged species *(2)* playing the role of adduct *(1)*:



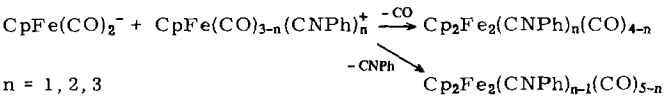
(2)

$$L_xMCNR^{(2-m)+} + L_yM'^{(2-n)-}$$

(3)

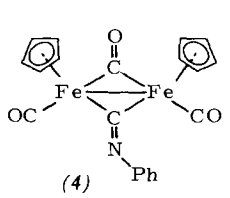
We have now accomplished the postulated reaction sequence consisting of "isocyanide bridge formation" (a) and "isocyanide transfer" [(a)+(b)].

Stable isocyanide bridges such as in *(2)*, which only occur in combination with a metal-metal bond[3], are known to exist, *e.g.* in the cyclopentadienyliron system. By proper choice of reactants—$CpFe(CO)_2^-$ as nucleophilic metal component and $CpFe(CO)_{3-n}(CNR)_n^+$ as electrophilic "heteroallene"— a systematic preparation of such dinuclear complexes should be possible:

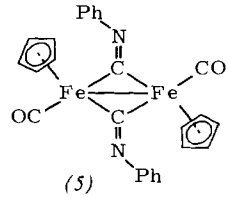


n = 1, 2, 3

As expected, the reactions (at −78 °C) come to a halt after bridge formation; elimination of carbonyl or isocyanide is followed by the formation of singly or doubly isocyanide-bridged complexes *(4)* and *(5)*. They can be separated from each other and from accompanying bis[dicarbonyl(η^5-cyclopentadienyl)iron] by chromatography on silica gel with dichloromethane.



(4)



(5)

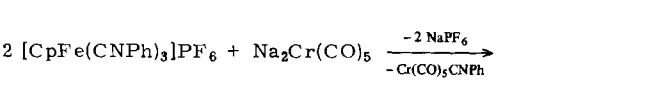
The product distribution [%] of the reactions of $CpFe(CO)_2^-$ with $CpFe(CO)_{3-n}(CNPh)_n^+$ is as follows:

n	$[CpFe(CO)_2]_2$	*(4)*	*(5)*
1	<5	73	—
2	5	27	28
3	<5	5	56

Compounds *(4)* and *(5)* were formerly obtained in very poor yields [*(5)*: 0.7%] from $[CpFe(CO)_2]_2$ and phenyl isocyanide[4a]. X-Ray structure analyses now available show *(4)* to have a *cis*(Cp)- and *(5)* a *trans*(Cp)-*anti*(Ph) configuration[4]. A trisubstituted isocyanide derivative of $[CpFe(CO)_2]_2$ could only be prepared with methyl isocyanide[5]; the fourth CO ligand completely resisted replacement by CNR.

It therefore was an attractive challenge to attempt the synthesis of $[CpFe(CNPh)(\mu\text{-}CNPh)]_2$ by our method. However, the $CpFe(CNPh)_2^-$ ion required as metallic base is unknown. In the general reaction scheme, the two-step process of "isocyanide transfer" (a)+(b) formally proceeds *via* transfer of an isocyanide dication from the Lewis acid metal (M') to the Lewis base metal (M) with concomitant liberation of an anionic species *(3)*. This suggests use of the cation $CpFe(CNPh)_3^+$ as Lewis acid metal component and of an anion such as $Cr(CO)_5^{2-}$ as isocyanide acceptor, which *cannot* form a stable dinuclear complex *(2)* with $CpFe(CNPh)_3^+$ but reacts according to (b). The $CpFe(CNPh)_2^-$ generated "*in situ*" should react immediately with excess $CpFe(CNPh)_3^+$ to give the desired neutral compound.

Reaction of *two* equivalents of $CpFe(CNPh)_3^+$ with *one* equivalent of $Cr(CO)_5^{2-}$ is in accord with this concept:



(6)

The stable tetrakis(phenyl isocyanide) complex *(6)* was characterized by elemental analysis, IR [(CH_2Cl_2) 2078, 1646 (s) cm^{-1}], ^{1}H-NMR [20 °C ($CDCl_3$, int. TMS; δ=4.71 (s, C_5H_5, 10H), 6.83—7.60 (m, C_6H_5, 20H)], and mass spectrum [*e.g.* M^+, $[Cp_2Fe_2(CNPh)_n]^+$ (*n*=0—3), $[CpFe(CNPh)_n]^+$ (*n*=0—3)]. X-Ray structure analysis is in progress.

Procedure

Solutions of $[CpFe(CNPh)_3]Cl$[6] (1.3 g, 2.8 mmol) and $Na_2Cr(CO)_5$[7] (0.33 g, 1.4 mmol) in tetrahydrofuran (100 ml each) are combined at −78 °C. The mixture is allowed to slowly warm to room temperature, and the dark violet solution

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[**] Isocyanide- and Heteroallene-Bridged Metal Complexes, Part 1. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

is evaporated to dryness. The residue is taken up in dichloromethane and chromatographed on silica gel: CH_2Cl_2 elutes $Cr(CO)_5CNC_6H_5$, and CH_2Cl_2/THF (1 : 1) pure *(6)*. Crystallization from CH_2Cl_2/pentane affords 0.32 g (35 %) of lustrous black-violet leaflets of m. p. 137—138 °C.

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German version: Angew. Chem. 90, 920 (1978)

[1] a) *M. G. Thomas, W. R. Pretzer, B. F. Beier, F. J. Hirsekorn, E. L. Muetterties*, J. Am. Chem. Soc. *99*, 743 (1977); b) *Y. Yamamoto, H. Yamazaki*, J. Organomet. Chem. *137*, C 31 (1977).
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1,2,3-Tri-*tert*-butylphosphirane Oxide and Its Thermal Decomposition into (*Z*)-2,2,5,5-Tetramethyl-3-hexene and *tert*-Butylphosphinidene Oxide[**]

By *Helmut Quast* and *Manfred Heuschmann*[*]

Phosphirane oxides have been invoked as intermediates in the base-induced rearrangement of α-halo phosphinic esters[1] and α-halo phosphane oxides[2]. Their ring strain makes them attractive precursors for generation of the hitherto rarely investigated phosphinidene oxides[3]. We report here on the synthesis, reactions, and thermolysis of the first phosphirane oxide *(3)*.

Reaction of 1 mol *tert*-butyldichlorophosphane with 3 mol 2,2-dimethylpropylmagnesium chloride in boiling ether/benzene (1 : 1) for 10 days and subsequent oxidation with hydrogen peroxide afforded phosphane oxide *(1)*[4], m. p. 125—126 °C, in 46 % yield. *(1)* was lithiated with 1.05 mol *sec*-butyllithium in tetrahydrofuran/2-methylbutane at −78 °C and then chlorinated with 1.2 mol tetrachloromethane at −100 °C to the diastereomeric α-chlorophosphane oxides *(2)* (30 : 70). Reaction of *(2)* with lithium diethylamide in ether at −80 °C to 0 °C led to ring closure and formation of phosphirane oxide *(3)* (*ca.* 80 %), accompanied by slight reduction to *(1)* and formation of the consecutive product *(4)*. Preparative layer chromatography (SiO_2/ether) and crystallization from pentane at −20 °C afforded 52 % *(3)* as colorless needles, decomp. pt. 119–120 °C; MS: $m/e = 244$ (3 %, M^+), 229 (3 %, $M-CH_3$), 188 (7 %, $M-C_4H_8$), 125 (16 %, C_9H_{17}), 97 (11 %, C_7H_{13}), 83 (20 %, C_6H_{11}), 70 (37 %, C_5H_{10}), 57 (100 %). The P=O frequency in the IR spectrum of *(3)* (1180 cm^{-1}) is 26 cm^{-1} higher than that of *(1)*. The symmetry of *(3)* and hence the *cis*-configuration of the *tert*-butyl groups attached to C-2 and C-3 are indicated by the NMR spectra (Table 1). Ring-closure drastically reduces the ^{31}P-coupling to the ring C-atoms[5] and strongly shifts the ^{31}P-signal towards high field (53.4 ppm) as observed in the case of 1,2,3-tri-*tert*-butyl-diazaphosphiridine oxide[6].

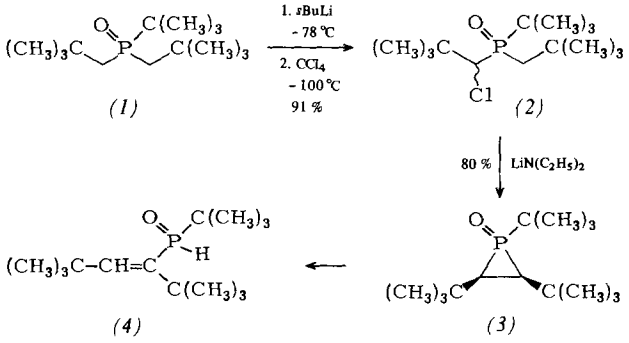


Table 1. NMR data of the phosphane oxides *(1)* and *(2)* and the phosphirane oxide *(3)* in [D]-chloroform. ^{31}P-coupling constants [Hz] in square brackets and multiplicity in the off-resonance decoupled ^{13}C-NMR spectra in round brackets.

Cpd.	δ(^{1}H) P-*t*Bu	C-*t*Bu	P—CH	δ(^{31}P) [a]
(1)	1.17 [13.4]	1.21	1.51 [6.6] 1.88 [9.8] $J_{AB}=15.4$	+52.16
(2) [b, c]	1.10 [13.7]	1.30 [0.5] 1.38	1.65 [7.6] 2.63 [12.4] $J_{AB}=16.0$	+56.62
(2) [c]	1.30 [14.2]	1.24 [0.4] 1.38	3.94 [3.8] 1.69 [6.2] 1.83 [8.9] $J_{AB}=15.4$	
(3)	1.25 [17.4]	1.27 [0.5]	4.26 [7.8] 1.63 [8.0]	−1.27

Cpd.	δ(^{13}C) P-*t*Bu	C-*t*Bu	P—CH
(1)	33.6 (s) [65.5] 24.5 (q)	32.5 (s) [4.4] 31.8 (q) [5.9]	39.5 (t) [58.8]
(2) [b]	34.7 (s) [64.0] 25.3 (q)	32.6 (s) [3.7] 37.9 (s) [1.5] 28.3 (q) [3.7] 32.1 (q) [5.9]	32.6 (t) [61.0] 62.4 (d) [51.5]
(3)	32.7 (s) [64.0] 25.6 (q) [1.5]	32.8 (s) [5.2] 32.2 (q) [6.6]	37.0 (m) [12.5]

[a] 85 % phosphoric acid as ext. standard (δ = 0). Negative values correspond to higher field. [b] Thermodynamically stable diastereomer. [c] ^{1}H-NMR spectrum in [D_6]-benzene.

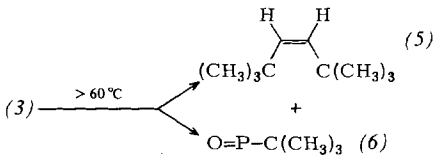
Compound *(3)* is remarkably stable towards concentrated hydrochloric acid. On reaction with strong bases, such as lithium piperidide or lithium diethylamide, *(3)* is slowly isomerized to *(4)*. In [D_6]-benzene[7] at 60 °C and above, *(3)* slowly decomposes quantitatively to (*Z*)-2,2,5,5-tetramethyl-3-hexene *(5)* as the sole identifiable product. *tert*-Butylphosphinidene oxide *(6)*, the second product expected to be formed along with *(5)*, could not be trapped with bis(trimethylsilyl)ethylene, 2,2-dimethylpropylidene-*tert*-butylamine, 2,3-dimethylbutadiene, 2,3-butanedione, or benzil. On the other hand, decomposition of *(3)* in methanol (20 h, 70 °C)[8] leads quantitatively to methyl phosphinate *(7)*[9]. Reaction of 2 mol 9,10-phenanthraquinone with 1 mol *(3)* in [D_8]-dioxane at 70 °C gave *(8)* in 50 % yield, which could also be prepared independently from 9,10-dihydroxyphenanthrene and *tert*-butylphosphonyl dichloride in boiling xylene in the presence of 2 mol triethylamine (70 %, m. p. 188—190 °C).

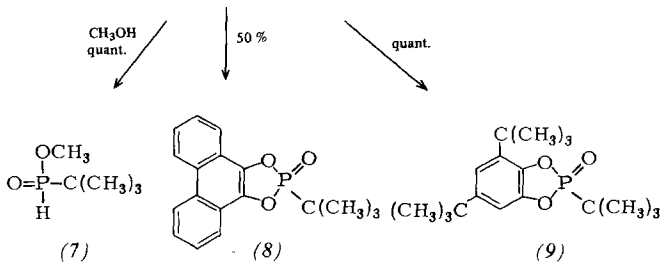
The presumed second thermolysis product *(6)* could be trapped quantitatively in [D_6]-benzene with 3,5-di-*tert*-butyl-

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[**] Three-membered Heterocycles, Part 5. This work was supported by the Fonds der Chemischen Industrie. The results constitute part of the forthcoming Dissertation by *M. H.*—Part 4: *H. Quast, F. Kees*, Chem. Ber. *110*, 1780 (1977).

1,2-benzoquinone (1 mol, 20 h, 75 °C) as compound *(9)*, which, by analogy with *(8)*, has been prepared from 3,5-di-*tert*-butyl-





1,2-dihydroxybenzene and *tert*-butyl-phosphonyl dichloride (65 %, m. p. 85—86 °C).

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CAS Registry numbers:
(1), 68108-82-7; *(2)*, 68108-83-8; *(3)*, 68108-84-9; *(4)*, 68108-85-0; *(5)*, 692-47-7; *(6)*, 68108-86-1; *(7)*, 34309-91-5; *(8)*, 68108-87-2; *(9)*, 68108-88-3; ^{13}C, 14762-74-4

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[4] The new compounds isolated gave correct elemental analyses and the expected IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, and mass spectra.

[5] In agreement with the trend observed in the case of cyclic phosphane oxides: *G. A. Gray, S. E. Cremer, K. L. Marsi*, J. Am. Chem. Soc. *98*, 2109 (1976).

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[7] Solutions of *(3)* were heated in sealed NMR sample tubes previously degassed at 10^{-5} torr.

[8] Thermolytically [3b] or photolytically [3c] generated phenylphosphinidene oxide also forms a phosphinate with methanol.

[9] *B. Krawiecka, J. Michalski*, Bull. Acad. Pol. Sci. Ser. Sci. Chim. *19*, 377 (1971); Chem. Abstr. *75*, 140944j (1971).

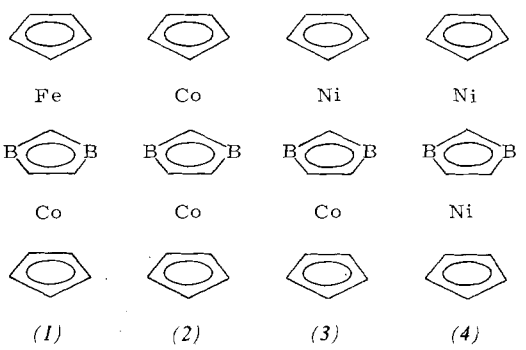
Paramagnetic Triple-Decker Sandwich Complexes[1]

By *Walter Siebert, Joseph Edwin*, and *Manfred Bochmann*[*]

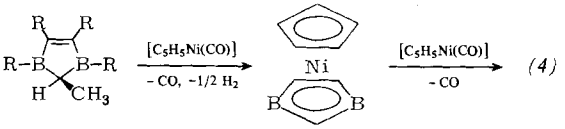
Dedicated to Professor E. O. Fischer on the occasion of his 60th birthday

The previously reported dinuclear complexes containing three parallel five-membered ring ligands[1] are diamagnetic and have 30[2a] or 34 valence electrons. EH calculations[3a] are available for the first triple-decker sandwich[2b], the $3(\pi^6)/2(d^8)$ ion $[(C_5H_5)_3Ni_2]^+$, from which a 30-electron/34 electron rule was derived[3]. We report here on the first paramagnetic triple-decker sandwich complexes *(2)*—*(4)* containing 31, 32, and 33 valence electrons.

Reaction of 1,3,4,5-tetraethyl-2-methyl-1,3-diborolene *(5)* with dimeric η^5-cyclopentadienyl(carbonyl)nickel as supplier



of the three-electron donor fragment $[(C_5H_5)Ni]$ leads to formation of the diamagnetic nickelocene analogue[4] *(6)* and small amounts (10—20 %) of deep-green (shiny-blue in thick layers) complex (4), which is obtained in almost quantitative yield on "stacking" *(6)* with $[(C_5H_5)Ni(CO)]_2$.



(5), R = C_2H_5 *(6)*

The new complex *(4)* is air-stable, readily soluble in nonpolar solvents, and crystallizes from ether/acetonitrile in thin platelets. Having 33 valence electrons the compound is expectedly paramagnetic ($\mu_{eff} = 1.52\,\mu_B$[5a]). In the ^{1}H-NMR spectrum it shows broad signals[5b] which shift in dependence of the potassium content in [D$_8$]-tetrahydrofuran/K solvent.

On reduction, the deep-red diamagnetic $(4)^-$ having 34 valence electrons is formed [^{1}H-NMR: $\delta = 4.83$ (s), 1.74 (q), 1.35 (s), 1.15 (t), 1.2—1.0 (m for B—C_2H_5); ^{11}B-NMR: $\delta = +5.6$ (in [D$_8$]-THF) rel. to $Et_2O \cdot BF_3$ and TMS int., resp.]. The appearance of only one C_5H_5 signal and a quartet for the C—C_2H_5 groups confirm the triple-decker sandwich structure of the anion $(4)^-$, which is rapidly oxidized with oxygen to *(4)*. The complex *(4)* reacts with $Ag^+BF_4^-$ to give the blue, paramagnetic 32 valence-electron triple-decker salt $(4)^+BF_4^-$ (two unpaired electrons). Electrochemical investigations on *(4)* confirm the reversible uptake and release of electrons[6].

The cobalt derivative *(3)* isoelectronic with $(4)^+BF_4^-$ is blue-green in solution, and, analogous to *(4)*, can likewise be prepared by "stacking" the sandwich *(6)* with $[(C_5H_5)Co(CO)_2]$, while *(2)*, which is yellow-green in solution, is obtained only in low yield on reaction of *(5)* with $[(C_5H_5)Co(CO)_2]$. Like *(1)*[7] and *(4)*, complexes *(2)* and *(3)* are air-stable and readily soluble in nonpolar solvents. Complexes *(1)* through *(4)* sublime in melting-point tubes above 130 °C and deliquesce between 220 and 270 °C. In the mass spectrum (70 eV), the molecular peak ($I_{rel} = 100\,\%$) appears in each case together with the expected isotopic pattern; only slight fragmentation is observed.

The bonding in complexes *(1)*—*(4)* and in $(4)^-$ can be considered in terms of the aromaticity and cluster formalisms. In each case there are three π^6-systems held together by two metal ions, which have 12 to 16 d electrons. In the MO diagram[3a] for the triple-decker the e_1' level in $(4)^-$ is completely occupied, as in $[(C_5H_5)_3Ni_2]^+$, while in *(2)* it is only singly occupied. According to the cluster description *(1)*—$(4)^-$ each contain a heptatomic *closo*-system C_3B_2MM', requiring 16 skeletal electrons according to the $(2n+2)$ rule[8]. In the case of *(1)* these are supplied by C(3 × 3), B(2 × 2), Fe(1), and Co(2). $(4)^-$ has four electrons more than *(1)*, so instead

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of the $(2n+2)$ rule the $(2n+6)$ rule for *arachno*-structures should apply. However, opening of the cage, as in the polyhedral boranes and carbaboranes, is not expected here[2a], but rather a widening of the metal-ring distance as predicted by the EH calculations as a consequence of the successive occupation of the weakly antibonding e_1' level.

The smooth formation of *(4)* from *(6)* and the fragment $[(C_5H_5)Ni]$ is a parallel to the "stacking" of nickelocene[2b, 3b] with $[(C_5H_5)Ni]^+$ to give the $[(C_5H_5)_3Ni_2]^+$ ion, from which $[(C_5H_5Ni)_2C_3B_2]^+$ is derived by replacement of two C by B atoms in the μ-ring.

$(4)^-$ is the second example of a 34-electron triple-decker sandwich with three five-membered rings as ligands. The first triple-decker sandwich ions with a C_8H_8 ring in the bridge position have recently been reported: the diamagnetic complexes $[(C_8H_8)_3Ti_2]^{2-}$[9a] and $[\{(C_5H_5)Co\}_2C_8H_8]^{2+}$[9b] likewise have 34 valence electrons.

μ-(1,3,4,5-Tetraethyl-2-methyl-1,3-diborolenyl)bis[η-cyclopentadienylnickel] (4)

A solution of *(6)*[4] (0.30 g, 0.96 mmol) and $[CpNi(CO)]_2$ (0.16 g, 0.53 mmol) in mesitylene (5 ml) is heated at 140—150 °C for 3 h. After removal of the solvent *(4)* is sublimed at 120—130 °C/0.01 torr. Yield 0.40 g (96 %).—High-resolution MS: $C_{22}H_{33}{}^{11}B_2{}^{58}Ni^{60}Ni$ 437.1431 (calc. 437.14294).

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[2] a) First examples: the isomeric $[\{(C_5H_5)Co\}_2C_2B_3H_5]$-complexes, see *D. C. Beer, V. R. Miller, L. G. Sneddon, R. N. Grimes, M. Mathew, G. J. Palenik*, J. Am. Chem. Soc. *95*, 3046 (1973); *R. Weiss, R. N. Grimes*, J. Organomet. Chem. *113*, 29 (1976); b) *H. Werner, A. Salzer*, Synth. Inorg. Met.-Org. Chem. *2*, 239 (1972).
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[5] a) We thank Dipl.-Chem. *W.-D. Griebler*, Marburg, for the measurement; b) δ = 37.3, −33.5, −8.5, −6.3, +7.5 and 8.1 (in $[D_8]$-toluene, rel. TMS int.). We thank Doz. Dr. *F. H. Köhler*, München, for recording the spectrum.
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Diorganodichlorophosphonium Hydrogen Dichlorides, a Novel Class of Compounds Containing $[ClHCl]^-$ Ions

By *Wilhelm Kuchen, Dietrich Mootz, Heinrich Somberg, Hartmut Wunderlich*, and *Hans-Georg Wussow*[*]

Dithiophosphinic acids of type *(1)* react with chlorine to give the corresponding diorganotrichlorophosphoranes *(2)*[1]. On carrying out this reaction with the *p*-methoxyphenyl-substituted acids *(1a)*—*(1c)*[2], however, we obtained the novel compounds *(3a)*—*(3c)* as products. They contain chlorine

$$RR'P(S)SH + 3Cl_2 \longrightarrow RR'PHCl_4 + S_2Cl_2$$
(1) *(3)*

$$(3) \xrightarrow[CHCl_3,\ 20°C]{N_2\text{-stream},\ 60°C} RR'PCl_3 + HCl$$
(2)

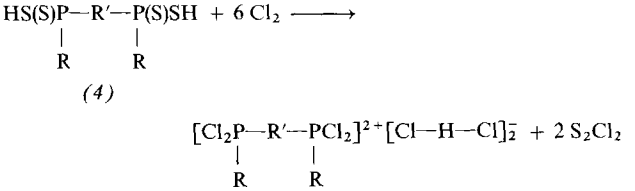
$R = 4\text{-}CH_3OC_6H_4$
$R' = CH_3$ *(a)*, C_6H_5 *(b)*, $4\text{-}CH_3OC_6H_4$ *(c)*

only in the oxidation state-1, and on hydrolysis give quantitatively the phosphinic acids RR'P(O)OH and hydrogen chloride.

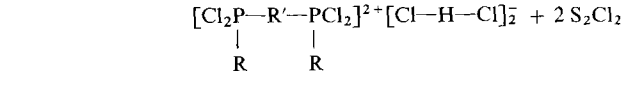
Passage of dry nitrogen through a boiling solution of *(3a)*—*(3c)* in trichloromethane leads to liberation of HCl and formation of the trichlorophosphoranes *(2a)*—*(2c)*, which react again with HCl gas at room temperature with regeneration of *(3)*. A compound of composition *(3)*, for which the structure $[(C_6H_5CH{=}CH)_2PCl_3H]^+Cl^-$ has been proposed, had already been obtained by reaction of PCl_5 with styrene[3].

The $^{31}P\{^1H\}$-NMR spectra of *(3a)*—*(3c)* each show only one singlet—in a region typical for phosphonium ions[4] [*(3a)*: δ = 104, *(3b)*: δ = 90.2, *(3c)*: δ = 88.8; saturated solution in $CDCl_3$ rel. to 85 % H_3PO_4]. The presence of penta- or hexacoordinated phosphorus can thus be ruled out. The ^1H-NMR spectra (saturated solution in $CDCl_3$) each show, *inter alia*, an acidic proton (δ = 12—13) and, for the methoxy group, a sharp singlet whose chemical shift and halfwidth is unchanged from that observed in the spectra of the corresponding HCl-free compound *(2)*. Since, in all cases, the FD-mass spectra also show signals for phosphonium ions $[RR'PCl_2]^+$ as peaks of highest intensity, we formulate *(3a)*—*(3c)* as diorganodichlorophosphonium hydrogen dichlorides $[RR'PCl_2]^+[ClHCl]^-$. In the IR spectrum (Nujol) of *(3a)* a band is observed at 1150 cm^{-1}, which from its position, halfwidth and intensity is assigned to the $2\nu_2$ deformation vibration of the $[ClHCl]^-$ ion. This band was accordingly absent in the case of *(2a)*, and was not observed in the IR spectra of *(3b)* and *(3c)* either. This finding, however, does not rule out a phosphonium hydrogen dichloride structure for the latter two compounds[5], which has been confirmed by X-ray structure analysis in the case of *(3a)*.

Analogous chlorination of the difunctional dithiophosphinic acids *(4a)* and *(4b)*[6] leads as follows



(4)



(5)

$R = 4\text{-}CH_3OC_6H_4$
$R' = 1,4\text{-}C_6H_4$ *(a)*, $-(CH_2)_4-$ *(b)*

to products, which according to their composition and properties are likewise hydrogen dichlorides (dichlorohydrogenates), namely *(5a)* and *(5b)*.

Experimental

A slow stream of chlorine gas is passed over a stirred solution or suspension of the acids *(1a)*—*(1c)* or *(4a)* or *(4b)* in CCl_4 at 0 °C in the absence of moisture until absorption ceases. The deep-red solution is decanted from the finely crys-

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talline precipitate, which is then repeatedly washed with ligroin (b. p. 30—50 °C). For further purification the hydrogen dichlorides *(3)* and *(5)*, respectively, are dissolved in a small amount of $CHCl_3$ and re-precipitated by slow addition of CCl_4 or ligroin (or in the case of *(3c)* by trimethylchlorosilane) (yield 60—90 %). Colorless needles, extremely sensitive to hydrolysis, soluble in $CHCl_3$, CH_2Cl_2, CH_3CN.

Crystal structure of (3a)

The substance forms monoclinic crystals, space group $P2_1/c$ with $a = 12.834(2)$, $b = 9.363(4)$, $c = 11.900(1)$ Å, $\beta = 113.46(1)°$; $Z = 4$. The structural determination with 1549 significant diffraction data led to an R value of 0.059. Figure 1[7] shows the tetrahedral phosphonium cation and the hydrogen dichloride anion together with the most important bond lengths [Å] and bond angles [°].

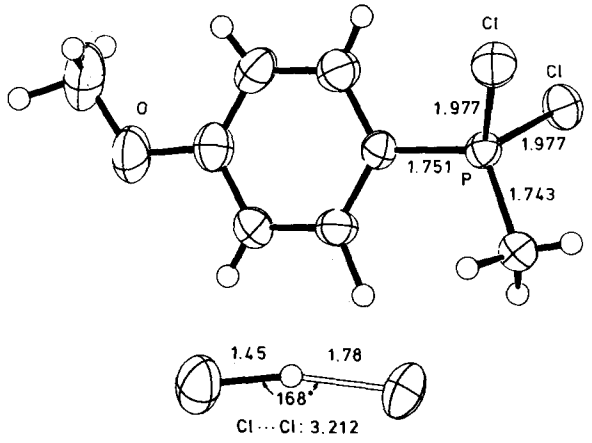


Fig. 1. Structure of dichloro(*p*-methoxyphenyl)methylphosphonium dichlorohydrogenate *(3a)*.

The anion appears asymmetric with respect to the position of the proton and not quite linear. This conclusion is uncertain owing to the high standard deviations (Cl—H 0.09 Å, Cl—H—Cl 6°). However, similar asymmetry has been observed by the more accurate method of neutron diffraction in $[(CH_3)_4N]^+[ClHCl]^-$, the only other reported example of a localized proton in this anion[8].

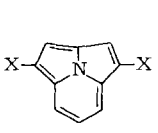
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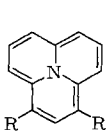
ABSTRACTS

This column contains abstracts of selected progress reports and review articles. Readers wishing to obtain the complete text of articles abstracted in this section are requested to approach a local library. A key to abbreviated source lists is provided in the Bibliographic Guide for Editors and Authors, published by Chemical Abstracts Service, Columbus, Ohio 43210, U.S.A.

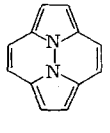
Cyclazines and related N-bridged annulenes are reported on by *W. Fritsch* and *U. Krämer*. Cyclazines are conjugated unsaturated cyclic molecules held planar by three covalent bonds to an internal N-atom. Stable cycl[3.2.2]azine *(1)* and its derivatives, which, *e.g.* can be prepared from indolizines or 3*H*-pyrrolizines, have aromatic character. On reaction with bromine, *(1)* is converted into the dibromide *(2)*. The unstable cycl[3.3.3]azine *(3)*, which is storable only under N_2, has been synthesized from quinolizinium salt *via* the ester *(4)*. Reaction of *(3)* with bromine vapor gives the dibromide of the cyclazine dication.—Cyclazines with additional heteroatoms in the skeletal structure, and annulenes containing hydrazine bridges, *e.g. (5)*, are also described. [Cyclazines and Related N-Bridged Annulenes. Adv. Heterocycl. Chem. *22*, 321—365 (1978); 123 references]



(1), X = H
(2), X = Br



(3), R = H
(4), R = $CO_2C_2H_5$



(5)

[Rd 47 IE]

Photosynthetic membranes as models for solar cells forms the theme of an article by *K. Sauer*. An examination of photosynthesis in plants suggests a set of design criteria which could be fulfilled, at least in part, in solar energy converters for commercial facilities: 1) Absorption of nearly all wavelengths of photochemically active radiation reaching the surface of the earth; 2) rapid and efficient conversion of electronic excitation for charge separation; 3) stabilization against wasteful charge recombination, the chemical species being separated *e.g.* by an impermeable membrane; 4) high conversion of the chemical potential into stable "chemical" products from readily available reactants (*e.g.* H_2O and CO_2). [Photosynthetic Membranes. Acc. Chem. Res. *11*, 257—264 (1978); 49 references]

[Rd 39 IE]

Coumarins in the Rutaceae are the theme of a review article by *A. I. Gray* and *P. G. Waterman*. The biogenesis, structural variants, and occurrence of simple coumarins as well as furano- and pyranocoumarins are described. In addition the compounds are discussed regarding their possible biological significance and their usefulness in taxonomic considerations. [Coumarins in the Rutaceae. Phytochemistry *17*, 845—864 (1978); 301 references]

[Rd 43 IE]

The fine control of the conversion of pyruvate (phosphoenolpyruvate) into oxaloacetate in various species is described in an article by *M. C. Scrutton*. Depending upon the species, the catalysts for this reaction are the enzymes pyruvate carboxylase, phosphoenolpyruvate carboxylase and phosphoenolpyruvate carboxytransphosphorylase. Owing to these enzymatic reactions, which enhance the supply of intermediates, the citric acid cycle can serve for both degradation as well as synthesis. Effectors for the above mentioned enzymes are acetyl coenzyme A and other acyl coenzymes A as well as glutamate, aspartate, and α-ketoglutarate. It is hoped that an investigation of the regulation will provide a detailed explanation of the biological function of the enzymes. [Fine Control of the Conversion of Pyruvate (Phosphoenolpyruvate) to Oxaloacetate in Various Species. FEBS Lett. *89*, 1—9 (1978); 60 references]

[Rd 44 IE]

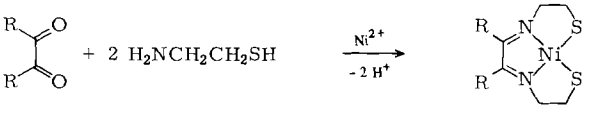
The connection between photosynthetic carbon reduction and photorespiration is discussed in an article by *T. J. Andrews* and *G. H. Lorimer*. The primary reaction of photorespiration consists of the oxidative cleavage of ribulose 1,5-bisphosphate *(1)* to give 3-phosphoglycerate and phosphoglycolate. Photorespiration thus counteracts, in part, the result of photosynthesis. The question arises whether this apparently meaningless debilitating effect on the plants might not be avoidable. The authors show with the aid of experimental findings that all carboxylases for *(1)* are at the same time also oxygenases for *(1)*. The ratio of carboxylation to oxygenation depends upon the relative concentrations of the substrates CO_2 and O_2. It would appear that photorespiration, though of no particular advantage to plants could not be dispensed with in the course of evolution because it is an unevadable consequence of the chemical structure of the active center of ribulose 1,5-bisphosphate carboxylase. [Photorespiration. Still Unavoidable? FEBS Lett. *90*, 1—9 (1978); 103 references]

[Rd 45 IE]

Steric aspects of dopaminergic drugs are dealt with in a report by *D. D. Miller*. At the physiological pH value, dopamine occurs in a variety of molecular species, the phenolic ammonium salt being predominant. Nevertheless, it is still unknown which of these forms is optimal for a dopaminergic action. Hence, a series of analogs which are fixed in their conformation and some more complex molecules with dopaminergic segments have been investigated. The experiments showed that the stretched form is optimal for binding to dopamine receptors, but also that rotamers have to be taken into consideration. The dopaminergic action is largely dependent upon the stereochemistry. [Steric Effects of Dopaminergic Drugs. Fed. Proc. *37*, 2392–2395 (1978); 33 references]

[Rd 46 IE]

Template reactions are the theme of a review by *M. de Sousa Healy* and *A. J. Rest*. Macrocycles were hitherto mainly accessible only *via* laborious routes and in small yields. One of the first examples of the ability of metals and metal ions to promote the formation of macrocycles was the self-condensation of *o*-phthalonitrile to give metal phthalocyanine complexes from which the free ligand was easily displaced. From



(1)

the formation of macrocycles such as *(1)* using Ni^{2+} ions it was recognized that the coordination sphere of the metal ion would hold the reacting groups in the correct positions for cyclization reactions, *i.e.*, the metal ion acts as a "template". K^+ has proven suitable for the synthesis of crown ethers, Ni^{2+} or Cu^{2+} are preferably used for the synthesis of planar macrocycles containing four nitrogen atoms. [Template Reactions. Adv. Inorg. Chem. Radiochem. *21*, 1—40 (1978); 143 references]

[Rd 48 IE]

The use of liquid crystals in chromatography is dealt with in an article by *H. Kelker*. Liquid crystals can be used as stationary phase in gas-liquid chromatography for the separation of isomers whose separation is not easy to achieve with normal isotropic liquids. An example is the resolution of a mixture of *m*- and *p*-xylene using liquid-crystalline 4,4-azooxyanisole. Otherwise, *m*- and *p*-xylene necessitate the use of highly efficient columns, *e.g.* modified bentonites, for their separation. The article contains, *inter alia*, a list of all the previous applications of liquid crystals as stationary phases in chromatography. [Liquid Crystals in Chromatography. Adv. Liq. Cryst. *3*, 237—273 (1978); references]

[Rd 49 IE]

BOOK REVIEWS

Biotransformation von Arzneimitteln (Bio-Transformation of Drugs). By *S. Pfeifer*, Verlag Chemie GmbH, Weinheim—New York. Vol. 1: 1977 reprint of the 1st edition of 1975, 484 pp., bound, DM 90.00. Vol. 2: 1st edition, 424 pp., bound, DM 70.00.

Volume 1 contains 329 monographs on the metabolism of various antibacterial sulfonamides, antidiabetic preparations, antiepileptic agents, psychopharmaceuticals, sedatives and hypnotics, and synthetic steroid hormones and estrogens with a different structure. The literature is covered up to 1972/73, and a literature supplement gives publications up to the middle of 1975.

Volume 2 contains 211 monographs on the metabolism of analgesics, antineuralgic drugs, antirheumatic preparations,

non-steroidal anti-inflammatory drugs, analgesic antagonists, drugs for arrhythmias, β-receptor blocking agents, antihypertensive agents, chemotherapeutic preparations (nitrogen-containing heterocyclic systems), coronary dilators, and tuberculostatics. The literature is covered up to 1973/74, and a literature supplement gives publications up to the middle of 1976. Besides, the references for volume 1 are also extended.

The third volume is expected to appear this year.

More and more work is being done on the biotransformation of drugs and the field is in a stage of rapid growth. It is therefore extremely difficult to give an account here that is both up to date and comprehensive.

The two volumes reviewed describe over 500 substances. This series of monographs differs from previous reviews by having a high information content and by being based on very recent literature; it is expected that the literature will be updated by special supplements in the following volumes.

Unfortunately, the naming of the substances is not uniform: the international short names are often used, but mainly in the Latin form (*e.g.* calcii benzamidosalicylas and acidum flufenamicum). This causes unnecessary confusion. Furthermore, it is difficult to see how the substances were selected: some of those which have been included are not yet used as drugs, or are no longer used in this way, while others that are very common (*e.g.* reserpine) are missing.

All the monographs are drawn up in the same form. In a condensed and clear manner, they give schemes of biotransformation, routes of elimination, and detection of metabolites in various species, together with the analytical methods used for this purpose. In a final section, called Remarks, we find *e.g.* incomplete or contradictory literature data. The author also gives supplementary data on individual metabolites (*e.g.* activity and distribution in the body) and—without any claims to completeness—further information *e.g.* on pharmacokinetics and drug interactions. In the presentation of this material, clearly no attempt was made to follow a systematic approach.

The collection can be recommended as a reference work for all those involved with the biotransformation of drugs.

K.-O. Vollmer [NB 433 IE]

Molecular Structure and Dimensions. Guide to the Literature 1935—1976. Organic and Organometallic Crystal Structures. Edited by *O. Kennard, F. H. Allen,* and *D. G. Watson* for the Cambridge Crystallographic Data Centre and the International Union of Crystallography. Bohn, Scheltema & Holtema, Utrecht 1977. 683 pp., bound, fl. 150.00.

While this volume, like the "60-year Structure Index" of "Structure Reports" consists of indexes (indexes of substance names, formulas, authors, and literature references), this time all the indexes have been developed with computer programs from the data bank of organic and organometallic crystal structures of the Cambridge Crystallographic Data Centre and printed from magnetic tape with photosetting. This is a prerequisite for greater up-to-dateness, variety, and reliability.

A substance name may contain many structural elements of a chemical compound. The index built up according to the KWIC (Keyword in context) concept records each compound under the word segment relevant to that compound and thus provides not only access to defined substances whose exact nomenclature is difficult but above all to related substances and groups of substances. In Part A are collected 10156 organic compounds and metal-containing organic compounds that include an interesting organic portion. One finds, for example, 49 adenine derivatives, 77 porphine derivatives and complexes, as well as 50 deuterated compounds. In Part B 5777 organometallic compounds and complexes are listed in two-fold arrangement: all the compounds of each metal are sorted again according to their relevant word segments, *e.g.* 139 phosphane complexes of platinum or 8 carbene complexes of chromium.

In Part A the molecular formula index lists all compounds in the usual way (C, H, all other elements in alphabetical order) but in Part B the formulas are permuted once more so that, *e.g.* all the fluorine or all the silicon compounds occur together. In both cases it is not always the true molecular formula that is used, but—when useful—partial molecular formulas of the "residues", *i.e.* of the discrete units of the compound. All the indexes lead, *inter alia*, directly to the original reference.

The printed book cannot offer the variety of entry that is provided in a data bank, because the extent and the cost force compromises. Victims of the compromises are keywords such as "hydrates" and "inclusion compounds", but also the possibility of finding in one place all the complexes of ligands such as salicylaldehyde or thiocyanate.

The reliability of the index is guaranteed by the programmed setting and automatic printing, provided that the basic material is faultless. To this end the material taken into the data bank is subjected on entry to numerous test programs. The logic of our language and spelling are, however, so complicated that variation in nomenclature and mode of writing must sometimes be recognized and corrected mentally, because heterogeneity in naming in conjunction with the strict logic of the sorting program leads sometimes to primitive errors on introduction into the index. The user accustomed to the working of a computer does not stumble over, for example, the separated positions of "vitamin B12" and "vitamin B(12)"; more serious is that compounds of the same type may be named according to different principles, *e.g.* "dichlorophthalocyanato-tin(IV)" or "stannic phthalocyanine".

Such failings are of little account when measured against the value of the total undertaking, and they are shared with traditionally prepared indexes. However, the data bank makes it possible to prepare cumulative indexes relatively easily, and when doing so to eradicate mistakes gradually during further developments of the programs.

Statistical data readily accessible by modern programming show by the numerous replications of the same structure, by the corrections to the data that become necessary, by the distribution of references in the original literature (which enables the completeness of the entries to be tested), and by the content of 28000 structures estimated for 1980 the importance now attaching to joint international efforts in connection with the collection and retrieval of scientific data. It is to be hoped that the development started with this project will not remain restricted to crystal structures.

Günter Bergerhoff [NB 440b IE]

Microbiological Aspects of Pollution Control. By *R. K. Dart* and *R. J. Stretton.* Elsevier Scientific Publishing Company, Amsterdam—Oxford—New York, 1977, 1st edit., vi, 215 pp., bound, Dfl. 85.00.

We read in a publication of the Fonds der Chemischen Industrie, dated October 27, 1977 that "This additional expense, necessitated by environmental protection, can become the 'eye of the needle' for productivity and research". This means that nowadays every chemist should know something about the microbial aspects of environmental protection. The book is aimed at engineers and therefore gives a detailed description of methods, *e.g.* for microbial water control, that have long been known to microbiologists and hygienists. The eleven chapters deal with the microbial formation of polluting compounds, atmospheric pollution and microorganisms,

health hazards of pathogenic microorganisms in water, testing water, effluent treatment, disinfection and the water cycle, eutrophication, thermal pollution, the sulfur cycle and waste recycling, oil pollution and biological degradation, the formation of organic mercury and arsenic compounds, reasons for the occurrence of nitrates, nitrites, and hydroxylamine in water, and the formation of carcinogenic nitrosamines and of aflatoxins.

While effluent treatment is described in detail, biodegradation receives too little space—a mere twenty pages for the degradation of aromatics, heterocyclics, alicyclics, synthetic detergents, and pesticides. The literature is basically confined to English and American sources. The book can be recommended as an introduction.

F. Lingens [NB 422 IE]

Comprehensive Biochemistry, Vol. 32: A History of Biochemistry. Part IV. Edited by *M. Florkin* and *E. H. Stotz*. Elsevier/North Holland Biomedical Press, Amsterdam, 1977. 1st edit., xx, 362 pp., 57 figs., bound, Dfl. 98.00.

This is the fourth part of the History of Biochemistry, a separate section of the Comprehensive Biochemistry series, and certainly the one least subject to change. With his historical sense that also characterizes his research in the field of biochemical evolution, dealing with the problems of cause and effect, *M. Florkin* knows very well how to present the parallel development of the concepts of chemistry and biochemistry—the mutual interdependence of nature and person, reality and perception. We saw in Part III[*] that ideas of nutrition had always been bound up with the concept of composition and decomposition, how the parts of the cell components are linked by basic chemical processes, the necessary energy being ensured by redox or group potentials *via* a common donor. This sets the scene, based on assimilation, dissimilation, and energetics, on which the processes of biosynthesis take place. Since the middle of the 18th century these have been developed in step with the advances of experimental and theoretical chemistry. The present volume deals with the early stages of present-day knowledge of the biogenesis of cell components and is illustrated by interesting portraits of many of the protagonists. The story begins with the application of mass and energy balances to living organisms and with the discovery of the assimilation of carbon dioxide by green plants. It ends with the introduction of isotope methods around the middle of the century, which made it possible to put the mechanisms of biosynthesis on a stronger foundation. It is exciting to find the intellectual sources and to learn about the philosophy and changing attitudes of biochemists, which enables us to understand and assess the various contributions in their proper historical context. The network of fruitful contacts during the period of elitist preoccupation with research problems (which seemed irrelevant to the wider public) and the personal contacts surviving the political tensions in the 18th and early 19th centuries—but also the emotional and national movements which influenced scientific thinking and which came in the next hundred years—give an instructive picture and shift the role and the inclination of many an outstanding research worker into a fitting and just perspective. At this time the possibility of reversing catabolic and anabolic processes was postulated as a result of mass action, and scientists discovered the fundamental biogenesis of urea and uric acid, "detoxication" processes as cellular activities, the β-oxidation of fatty acids, and the inability of the body to form certain amino acids. These observations, to which a great number of life scientists in many countries have made important contributions, fill the book with exciting material. The account is written in an elegant style and with warmth, and gives a stirring panorama, which makes us await the last volume with great interest. With its facts, interpretations, references, and portraits, this book is—and will no doubt long remain—a rich source for all who are interested in the history and philosophy of natural sciences.

L. Jaenicke [NB 429 IE]

[*] Angew. Chem. Int. Ed. Engl. *14*, 719 (1975); cf. also *17*, 699 (1978).

Immunologie (Immunology). By *G. Bundschuh* and *B. Schneeweiss*. Gustav Fischer Verlag, Stuttgart—New York 1976. 1st edit., xxxiv, 451 pp., linen, DM 42.00.

More than 2000 keywords from the field of immunology are arranged alphabetically in this book and explained briefly, in some cases with references to the original literature. It is certainly not possible to say that the fundamental principles of the immune system could be reconstructed from this collection. For this purpose the book is too concerned with human and clinical immunology, the quality of the individual sections is too varied, and the reported state of knowledge is a couple of years out of date (in this connection it may be mentioned that under the keyword "network theory" one finds a description of the mechanism of the serological precipitin reaction but not that of a general regulation principle based on receptor interactions). Many fundamental aspects of the immune system do not come over clearly, for example the recognition that regulation of the immune apparatus is based to a large extent on cell interactions: one looks in vain for keywords such as "cell interaction", "cooperation", and the like. On the other hand, the book contains a wealth of information that for a non-specialist is often difficult to find (even within the area of immunology). Working myself in "fundamental" immunology, I was particularly struck by the fact there were often very informative sections on matters important in clinical immunology. Summarizing, this is a book in which much can be looked up but in which much is presented incompletely or omitted. A useful supplementary book.

K. Rajewsky [NB 435 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal. All the publications listed are available through Buchhandlung Chemie, Boschstrasse 12, D-6940 Weinheim (Germany).

Surfactants and Interfacial Phenomena. By *M. J. Rosen*. John Wiley & Sons, London 1978. xiv, 304 pp., bound, £ 15.90.—ISBN 0-471-73600-7

Quantitative Drug Design. A Critical Introduction, Vol. 8. By *Y. C. Martin*. Marcel Dekker, New York 1978. x, 425 pp., bound, SFrs. 105.00.—ISBN 0-8247-6574-5.—A volume in the series "Medicinal Research Series"

Ozonation in Organic Chemistry, Vol. 1: Olefinic Compounds. By *Ph. S. Bailey*. Academic Press, New York 1978. xiv, 272 pp., bound, $ 28.50.—ISBN 0-12-073101-0

Chalcopyrite. Its Chemistry and Metallurgy. By *F. Habashi.* McGraw-Hill Book Company, New York 1978. xi, 165 pp., bound, DM 57.60.—ISBN 0-07-025383-8

Anorganische Chemie. By *H. P. Latscha* and *H. A. Klein.* Heidelberger Taschenbücher, Band 193. Springer-Verlag, Heidelberg 1978. xiii, 424 pp., paper, DM 24.80.—ISBN 3-540-08630-7

The Spectrum in Chemistry. By *J. E. Crooks.* Academic Press, London 1978. x, 313 pp., bound, £ 12.60.—ISBN 0-12-195550-8

Nomenklatur der Organischen Chemie. By *D. Hellwinkel.* Heidelberger Taschenbücher, Band 135. Springer-Verlag, Heidelberg 1978. 2nd Edition. viii, 170 pp., paper, DM 19.80.—ISBN 3-540-08796-6

Synthetic Methods of Organic Chemistry, Vol. 32. Edited by *W. Theilheimer.* S. Karger, Basel 1978. xv, 593 pp., bound, SFrs. 490.00.—ISBN 3-8055-2818-3

Valency. By *M. F. O'Dwyer, J. E. Kent,* and *R. D. Brown.* Springer-Verlag, Heidelberg 1978. 2nd Edition. xi, 251 pp., paper, DM 23.50.—ISBN 3-540-90268-6

Internal Rotation and Inversion. By *D. G. Lister, J. N. MacDonald,* and *N. L. Owen.* Academic Press, London 1978. xii, 246 pp., bound, £ 11.50.—ISBN 0-12-452250-5

Laseranwendungen in der Experimentalchemie.—Ein Praktikum. By *R. Schwankner.* Carl Hanser Verlag, München 1978. 177 pp., paper, DM 24.00.—ISBN 3-446-12576-0

Aldehydes.—Photometric Analysis, Vol. 5: Formaldehyde Precursors. By *E. Sawicki* and *C. R. Sawicki.* Academic Press, London 1978. xi, 408 pp., bound, £ 22.00.—ISBN 0-12-620505-1

Wood as an Energy Resource. By *D. A. Tillman.* Academic Press, New York 1978. xiv, 252 pp., bound, $ 13.50.—ISBN 0-12-691260-2

General and Synthetic Methods, Vol. 1. Senior Reporter: *G. Pattenden.* The Chemical Society, London 1978. xiii, 445 pp., bound, DM 150.00.—ISBN 0-85186-900-9. A volume in the series "Specialist Periodical Reports".

Thin Films. Interdiffusion and Reactions. Edited by *J. M. Poate, K. N. Tu,* and *J. W. Mayer.* John Wiley & Sons, New York 1978. x, 578 pp., bound, £ 25.00.—ISBN 0-471-02238-1

Inorganic Chemistry of the Transition Elements, Vol. 6. Senior Reporter: *B. F. G. Johnson.* The Chemical Society, London 1978. xiv, 503 pp., bound, DM 175.00.—ISBN 0-85186-550-X.—A volume in the series "Specialist Periodical Reports".

Chemical Reaction Engineering Reviews—Houston. ACS Symposium Series 72. Edited by *D. Luss* and *V. W. Weckman, Jr.* American Chemical Society, Washington 1978. vii, 331 pp., bound, $ 23.50.—ISBN 0-8412-0432-2

Erzeugnisse aus Ungarn. Produktion, Forschung und Entwicklung, Vertrieb. Edited by *S. Solt.* Verlag der Ungarischen Akademie der Wissenschaften, Budapest 1978. 390 pp., bound, DM 67.20.—ISBN 963-205-070-3

Explosionen. Ablauf und Schutzmaßnahmen. By *W. Bartknecht.* Springer-Verlag, Heidelberg 1978. x, 264 pp., bound, DM 148.00.—ISBN 3-540-08675-7

Advances in Carbohydrate Chemistry and Biochemistry, Vol. 35. Edited by *R. S. Tipson* and *D. Horton.* Academic Press, New York 1978. x, 433 pp., bound, $ 41.00.—ISBN 0-12-007235-1

Coordination Chemistry, Vol. 2. ACS Monograph Series 174. Edited by *A. E. Martell.* American Chemical Society, Washington 1978. x, 636 pp., bound, $ 90.00.—ISBN 0-8412-0292-3

Chromatography of Synthetic and Biological Polymers, Vol. 2: Hydrophobic, Ion Exchange and Affinity Methods. Edited by *R. Epton.* Ellis Horwood, Chichester 1978. vii, 353 pp., bound, £ 18.50.—ISBN 0-85312-073-0

Polymer Stress Reactions, Vol. 1: Introduction. By *A. Casale* and *R. S. Porter.* Academic Press, New York 1978. xvii, 118 pp., bound, $ 21.00.—ISBN 0-12-162801-9

Amino-acids, Peptides, and Proteins, Vol. 9. Senior Reporter: *R. C. Sheppard.* The Chemical Society, London 1978. xxi, 560 pp., bound, DM 155.00.—ISBN 0-85186-084-2.—A volume in the series "Specialist Periodical Reports".

The Donor-Acceptor Approach to Molecular Interactions. By *V. Gutmann.* Plenum Press, New York 1978. xvi, 279 pp., bound, $ 33.00.—ISBN 0-306-31064-3

Vogel's Textbook of Practical Organic Chemistry. Revised by *B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith,* and *A. R. Tatchell.* Longman, London 1978. 4th Edit. xxxv, 1368 pp., bound, £ 17.50.—ISBN 582-44250-8

Practice of Thin Layer Chromatography. By *J. C. Touchstone* and *M. F. Dobbins.* John Wiley & Sons, London 1978. xxiii, 383 pp., bound, £ 14.05.—ISBN 0-471-88042-6

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Multistage Organic Redox Systems—A General Structural Principle

By Klaus Deuchert and Siegfried Hünig[*]

A general structural principle for organic compounds that have the capacity for two-stage electron transfer is based on the following reaction sequence:

$$\underset{\text{RED}}{\ddot{X}\text{-}(\text{CH=CH})_n\ddot{X}} \underset{+e}{\overset{-e}{\rightleftharpoons}} \underset{\text{SEM}}{\ddot{X}\text{-}(\text{CH=CH})_n\overset{\oplus}{\ddot{X}} \leftrightarrow \overset{\oplus}{\ddot{X}}\text{-}(\text{CH=CH})_n\ddot{X}} \underset{+e}{\overset{-e}{\rightleftharpoons}} \underset{\text{OX}}{\overset{\oplus}{X}\text{=}(\text{CH-CH})_n\overset{\oplus}{X}}$$

In this scheme one or both of the entities X may be replaced by $Y^{\ominus}$. The radical partners in these systems often have very high thermodynamic stability. The choice of the end groups X and Y, (partial) inclusion of π-systems in rings, alteration of the number of vinylene groups, and aza-substitution make many variations possible. By means of this general structural principle numerous known compounds are brought together and new redox systems are simultaneously set up. The aim of the present review is to demonstrate the broad applicability of this principle, to indicate its significance for science and industry, and to describe some reactions.

1. Reduction and Oxidation—Two Changeable Concepts

Although oxidation and reduction are age-old chemical phenomena, it required centuries before the two concepts could be described from a uniform point of view, on the basis of the "phlogiston" theory[1], according to which phlogiston is *evolved* during combustion of a metal and *taken up again* during its regeneration. After the discovery of oxygen by *Scheele* and *Priestley*, it was *Lavoisier* who, in 1774, showed these ideas to be incorrect and since that time the uptake and removal of oxygen were considered as the characteristic features of oxidations and reductions. This narrow viewpoint persisted even after the development of the ionic theory at the end of the nineteenth century, and only slowly were the concepts of oxidation and reduction expanded and finally defined as the *loss* and the *uptake* of electrons[2], or better as electron *transfer*. Incidentally, in this definition phlogiston has reappeared unnoticed in a new guise.

In the field of *molecular* chemistry, and in particular hydrocarbon-based organic chemistry, the concepts of *oxidation* and *reduction* have remained largely associated with the *uptake* or *loss* of oxygen or with the *loss* or *uptake* of hydrogen.

The special role of hydrogen in reactions shown in equations (a) and (b) is in line with the ideas of hydrogenation and dehydrogenation, which are shown by equation (c) to be also valid if the overall reaction consists formally of the loss or uptake of oxygen[3].

$$H_3C\text{-}CH_3 \underset{+2H}{\overset{-2H}{\rightleftharpoons}} H_2C\text{=}CH_2 \qquad \text{(a)}$$

$$R\text{-}CH_2OH \underset{+2H}{\overset{-2H}{\rightleftharpoons}} R\text{-}C(=O)H \qquad \text{(b)}$$

$$R\text{-}C(=O)H \underset{-H_2O}{\overset{+H_2O}{\rightleftharpoons}} R\text{-}C(OH)_2H \underset{+2H}{\overset{-2H}{\rightleftharpoons}} R\text{-}C(=O)OH \qquad \text{(c)}$$

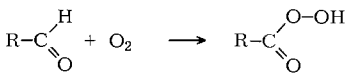
$$Cl^{\bullet} + C_6H_5CH_3 \longrightarrow C_6H_5CH_2^{\bullet} + HCl \qquad \text{(d)}$$

$$(C_6H_5)_3C^{\oplus} + C(H)(OR)_2H \longrightarrow (C_6H_5)_3C\text{-}H + HC(=O^{\oplus}\text{-}R)(O\text{-}R) \qquad \text{(e)}$$

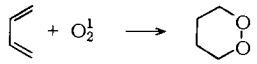
[*] Dr. K. Deuchert, Prof. Dr. S. Hünig
Institut für Organische Chemie der Universität
Am Hubland, D-8700 Würzburg (Germany)

Not only reactions of molecular hydrogen, but also transfer of H atoms [eq. (d)] or hydride ions [eq. (e), see also $NAD^{\oplus} + H^{\ominus} \rightleftarrows NADH$[4]] are covered by these concepts.

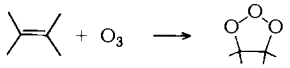
In contrast to the above hydrogen transfers, there are only a few reactions with triplet or singlet oxygen [eqs. (f)—(g)][5] and with ozone [eq. (h)] that could be regarded as "true oxidations".



(f)



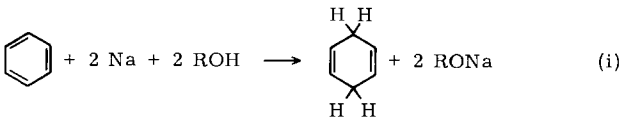
(g)



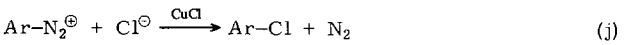
(h)

In none of these cases does it appear reasonable to consider the electron transfer separately from the element transfer.

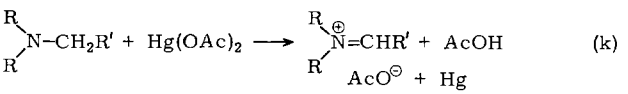
Nevertheless, each case must be considered separately, for in reactions according to equations (i)[6], (j)[7], and (k)[8]—which correspond formally to the reactions discussed above—electron transfer is known to occur first, followed by rapid making and breaking of bonds. For the hydroquinone ⇄ quinone transformation [eq. (l)] the rates of the *proton* and *electron transfer* are accurately known[9].



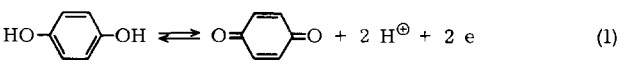
(i)



(j)



(k)



(l)

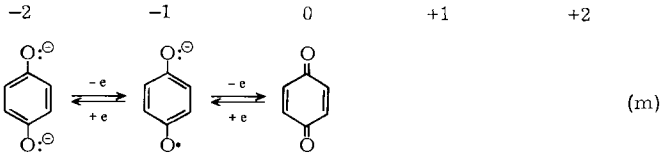
Among *organic compounds*, redox processes come into consideration as mere electron transfers only when no formation or rupture of electron-pair single bonds is required. In this case, stepwise transfer of single electrons must in principle be taken into account. It is the aim of this review to show that such multistage electron transfers are more common among organic compounds than is often assumed.

The following account will first describe the structural principle for compounds in which multistage electron transfer is to be expected. This general structural principle will then be explained with a large number of apparently unrelated examples.

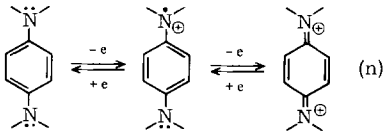
2. Two-Stage Redox Systems with Similar Fundamental Structure

2.1. Derivation of a General Structural Principle

Two-stage redox systems with stable radical ions were used unrecognized by chemists for almost 50 years, for the dye salt[10] discovered by *Wurster* in 1879 was recognized only in 1925 by *Weitz* (by a molecular weight determination[11]) as consisting of radical cations in the system shown in eq. (n). Owing to the complication of quinhydrone formation,



(m)



(n)

the radical anion ("semiquinone") formed initially on reduction of quinone was in fact found only in 1938 by *Michaelis*[12] in the redox system of eq. (m).

For the sake of clarity in the following discussion, the radical ion will be written with a fixed single electron, although its strong delocalization is mainly reponsible for the stability of such radical ions, as emphasized by *Weitz*[11,13]. *Weitz* also developed a general structure in which the existence of stable radical ions is to be expected[11,13]. The following structural principle can easily be developed on the basis of these facts:

Reversible redox reactions with transfer of two electrons in two separate steps (stages) are to be expected with compounds in which the end groups X and Y of the reduced form (RED) 1) have free electron pairs or π-systems[14,15] *available and 2) are connected by vinylene groups (n=0,1,2...).*

These structures, shown in equations (p) to (r), have largely "localized" π-systems in the RED and OX stages. In the SEM stage, however, the single electron is strongly delocalized; thus, from eq. (o) (a = charge on the compound), the following can be expected for the SEM form:

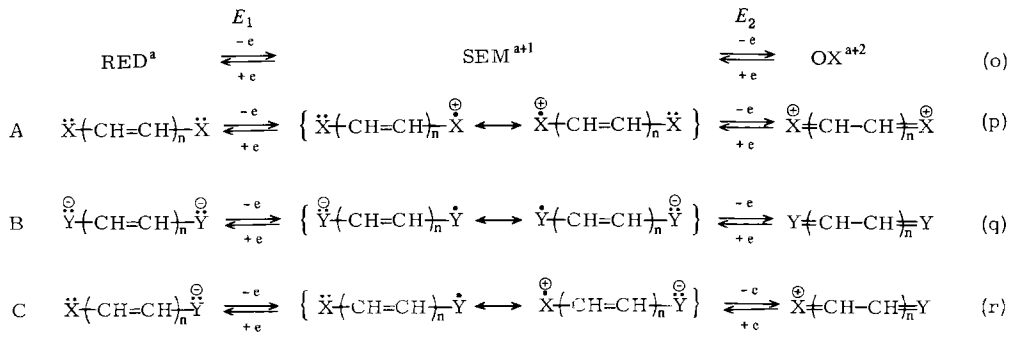
1) Measurable thermodynamic stabilization of the radical (ion) in comparison with similar radical systems in which the unpaired electron is not delocalized; and 2) particularly long-wave UV/VIS absorption as a consequence of the delocalization of the radical electron.

The systems A and B differ only by two charges; otherwise they are iso-π-electronic. The SEM radical appears as a cation in A and as an anion in B.

System C can be formally obtained by "crossing" systems A and B, whereby the same halves of A and B are joined together. By this device the RED and OX stages become respectively monoanions and monocations, while SEM becomes a neutral radical. *Katritzky*[16] regards such radicals as "merostabilized", relating the radicals in systems A, B, and C to cyanine, oxonol, and merocyanine dyes. Because of their dissymmetry (dipolar limiting forms), the radicals of system C should have a lower stability than the comparable radical ions of systems A and B. All three redox systems are capable of many variations:

1) Variation of X and Y (N, O, S, P, π systems),

2) Variation of the number of vinylene groups ($n=0,1,2,...$),



3) Variation of the vinylene groups by introduction into ring systems:
   a) both end groups are substituents of the ring systems,
   b) both end groups are part of the ring systems,
   c) one end group is part of the ring systems, and
4) Aza substitution of methine groups.

All these variations are treated in the following sections by means of examples from widely varying classes of compounds. In this way it should become clear that the general structural principle has a broad range of applicability and that apparently unrelated results can be rationalized by a general ordering principle.

The systems under discussion are presented in the following sections in the SEM radical stage. If the RED and OX stages are also known, these are noted under the formulae. Where these oxidation stages have not been isolated, their existence has been demonstrated by spectroscopic (NMR, UV/VIS, ESR) and electrochemical methods (polarography, cyclic voltammetry). As far as it is known, the semiquinone formation constant K [eq. (t)] is given, determined from the redox potentials according to eq. (s).

$$E_1 - E_2 = 0.059 \log K \quad (K, 25\,^\circ C) \qquad (s)$$

$$K = [SEM]^2/([RED][OX]) \qquad (t)$$

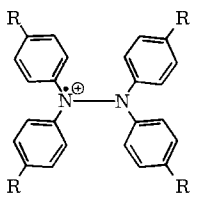
K describes quantitatively the thermodynamic stability of the SEM radical within the redox system; the very different kinetic stability (persistence) cannot be obtained from K.

2.2. Open-Chain Vinylogous Redox Systems

All redox systems of types A—C [eqs. (p)—(r)] in which neither the end groups nor the vinylene groups belong to a cyclic π-system are designated as "open-chain".

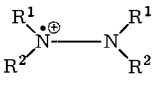
Systems with $n=0$, in which the end groups are therefore bonded directly to one another, also belong to this class. In this case hydrazine derivatives result if the end groups are nitrogen. It is certainly no accident that as early as 1927 *Weitz* isolated the first hydrazinylium salts *(1)* (type A, $n=0$)[17]. The aryl groups undoubtedly contribute to the stabilization[17b], for the short-lived tetraalkylhydrazinylium ions *(2)* can be detected only by ESR spectra and by their RED/SEM potentials. The reversible further oxidation to the dication $OX^{2\oplus}$ has not yet been achieved[18–20]; the energy requirements are clearly too high, because of the proximity of the charges.

A, n = 0



(1)

RED, SEM



(2)

RED, SEM



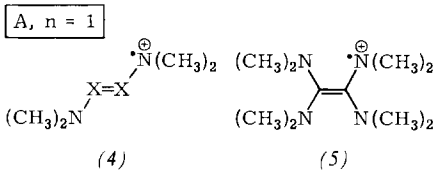
(3)

RED, SEM, OX

Formally, 1,5-dithiacyclooctane can be included here, for it is oxidized by nitrosyl tetrafluoroborate with S—S bond formation to give the long-lived radical cation *(3)*[21]; an excess of the oxidizing agent even gives the related dication[21].

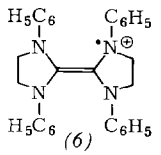
Members of type A, $n=1$ that have been intensively investigated are, besides derivatives of vinylenediamine *(4a)*[22a] and tetramethyltetrazene *(4b)*[22b], especially derivatives of vinylenetetraamine *(5)*[23] and *(6)*[24]; here the phenyl groups also prolong the lifetime of the SEM radical stage.

A, n = 1



(4)

(5)



(6)

(4a), X = CH RED, SEM

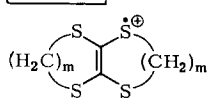
RED, SEM, OX

RED, SEM, OX

(4b), X = N RED, SEM

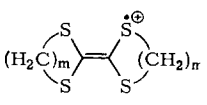
Sulfur is also a suitable end group[25], since, during the two-step oxidation by rapid cyclic voltammetry, the isomeric radical cations *(7)* and *(8)* can be clearly detected. On longer electrolysis, however, only the radical cations *(8)* are obtained, since *(7)* rearranges to *(8)*, presumably *via* the OX stage[26].

A, n = 1



(7), m = 2, 3

RED, SEM, OX



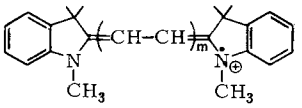
(8), m = 2, 3

RED, SEM, OX

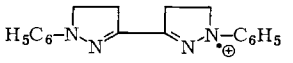
Example *(9)*, $m=1$[27], should be regarded as an open-chain redox system of type A, $n=2$, since the five-membered rings in which the end groups are included cannot influence the conjugation of the vinylene groups. The bipyrazolinyl

derivative *(10)*[28] can be regarded as a diaza compound of type A, $n=2$. To date *(10)* is the sole example of bis-aza

A, n = 2



(9), $K = 10^{6}$-10^{-2}(m = 1-5)
RED,SEM, OX

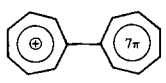


(10), $K = 10^{8.64}$
RED, SEM, OX

substitution next to the end groups. In both *(9)* and *(10)* the aromatic groups undoubtedly contribute to the thermodynamic stability of the SEM stage; thus, in *(9)*, $m=1$, about 20% of the spin density is found in the annelated benzene ring[27b]. The influence of additional vinylene groups in *(9)*, $m=1$—5, has been studied in detail[27a].

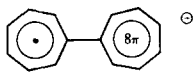
π-Systems are particularly suitable as end groups if cyclic systems with higher stabilization energy are produced at the RED or OX stage. Thus, oxidation of heptafulvalene affords initially the radical cation *(11)*[29], which can be included in type A, $n=0$. Admittedly, heptafulvalene is also reducible—by potassium, even in three stages[29b, 30]; whether the symmetrical radical anion may still be recorded as *(12)*[29b] is left an open question.

A, n = 0



(11)
RED, SEM, OX

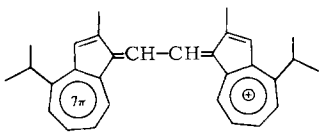
B, n = 0



(12)
SEM, OX

If azulene is regarded as a kind of derivative of tropilidene, then the very stable SEM form *(13)*[31] can be considered as a vinylog of *(11)*.

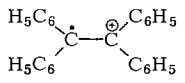
A, n = 4



(13)
RED, SEM, OX

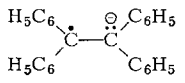
In tetraphenylethylene the phenyl groups are regarded as end groups; its two-stage oxidation passes through the radical cation *(14a)*[32a]; the reduction leads to the red radical anion *(14b)* (ESR)[32b].

A, n = 1



(14a), $K = 3 \cdot 10^{4}$
RED, SEM

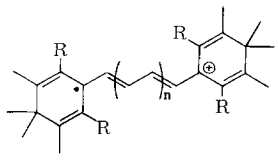
B, n = 1



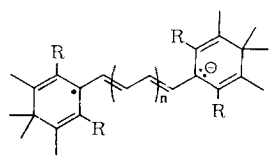
(14b)
OX, SEM

A special position is occupied by polyenes with cross-conjugated double bonds as the end groups. These polyenes can not only be oxidized polarographically in two stages but can also be reduced polarographically in two stages, no additional stabilization by cyclic conjugation being possible[33]. Thus, they appear as radical ions *(15)*, *(16)*, *(17)*, and *(18)* belonging to type A and also as *(19)*, *(20)*, *(21)*, and *(22)* belonging to type B[34]. Probably an important role is played in the stabilization of the radical ions by the pentadienyl cation, radical, and anion[35]. Disturbed coplanarity in these systems for $R=CH_3$ is signalized by strongly reduced stability of the radical ions.

A, n = 1-4



B, n = 1-4

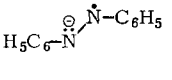


	n	K_{SEM} $R=CH_3$	K_{SEM} $R=H$		n	K_{SEM} $R=CH_3$	K_{SEM} $R=H$
(15)	1	2.5×10^{1}	3×10^{8}	*(19)*	1	— [a]	4×10^{12}
(16)	2	8.1×10^{1}	2.5×10^{5}	*(20)*	2	— [a]	9×10^{9}
(17)	3	1.4×10^{2}	2×10^{3}	*(21)*	3	— [a]	8×10^{8}
(18)	4	4×10^{0}	2×10^{1}	*(22)*	4	4×10^{7}	4×10^{7}

[a] Only OX/SEM reversible.

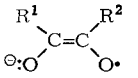
Long-known compounds are found also as type B of open-chain redox systems. The simplest system with $n=0$ consists of the dianion of azobenzene (RED) and azobenzene (OX), whose middle oxidation stage SEM occurs as the planar radical anion *(23)*[36].

B, n = 0

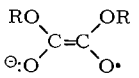


(23), $K = 2.7$
RED, SEM, OX

B, n = 1



(24)
RED, SEM, OX

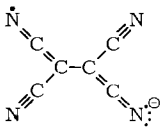


(25)
RED, SEM, OX

Furthermore, the very ready formation of the semidiones *(24)* by oxidation of α-hydroxy ketones or reduction of 1,2-diketones becomes understandable if one regards them as examples of type B, $n=1$, with oxygen as the end groups. For this class of substances extensive material is available[37], for which ESR-spectroscopic elucidation of the *E*/*Z* isomerism and conformational analysis of alicyclic systems were used. The same is true for the bisalkoxy semidiones *(25)* derived from oxalic esters[38].

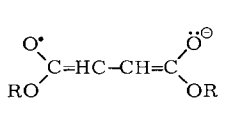
If the cyano group is regarded as an end-group unit then, for example, tetracyanoethylene should be included as the OX form of a two-stage redox system of type B, $n=1$, whose very stable radical anion *(26)* has long been known[39]. It should be regarded as a counterpart to the radical cation

B, n = 1

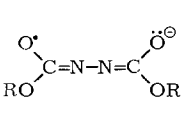


(26)
SEM, OX

B, n = 2



(27)
RED, SEM, OX

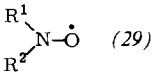


(28)
RED,SEM, OX

(5). As *E/Z* isomers, the radical anions *(27)*[40] derived from fumaric and maleic esters have different ESR spectra. The diaza derivative of *(27)*, namely the green radical anion *(28)* of the azodicarboxylic ester (OX), is also formed as stable intermediate on reduction to the RED stage[41].

The redox behavior of open-chain compounds of type C does not yet appear to have been studied. The extensive class of aminyl oxides *(29)*, however, could be included as the SEM radical stage in system C, $n=0$, although σ-radicals exist in this case[42].

C, n = 0



(29)

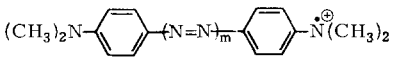
2.3. Redox Systems with Cyclic π-Systems between the End Groups

2.3.1. Two-Stage Wurster-Type Redox Systems

Two-stage redox systems are said to be of the Wurster type if their end groups are located outside a cyclic π-system that has an aromatic character in the reduced form.

Characteristic examples of the Wurster type have already been given in equations (m) and (n). The systems derived from *o*- and *p*-phenylenediamine are so well known from *Michaelis*' extensive investigations that reference to equation (n) is sufficient. *(30)*[43], *(31)*[44], and *(32)*[45] serve as special examples of radical cations of type A with nitrogen end groups. (The formal number of vinylene groups is derived from the shortest possible connecting line between the end groups.)

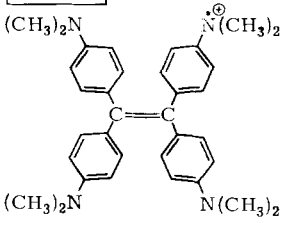
A, n = 4, 5



(30), m = 0
(31), m = 1

RED, SEM, OX

A, n = 5

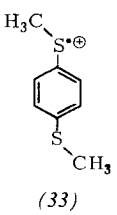


(32)

RED, SEM, OX

Sulfur and oxygen can also act as end groups for cationic redox systems of the Wurster type, as shown in *(33)*[46] and *(34)*[47].

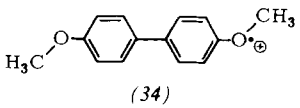
A, n = 2



(33)

RED, SEM

A, n = 4

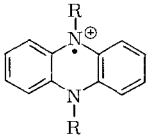


(34)

RED, SEM, OX

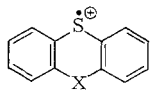
A special position[48] is occupied by the radical cations *(35)*[49] and *(36)* derived from phenazine, phenothiazine, phenoxathiin, and thianthrene, because they could also be included among the Weitz type (see Section 2.3.3)[49]. *(36a)*[50] is orange, *(36b)*[51] is blue-violet, and *(36c)*[52] is blue.

A, n = 1



(35)

RED, SEM

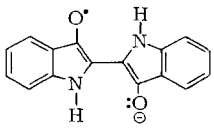


(36a), X = NR; *(36b)*, X = O;
(36c), X = S

RED, SEM

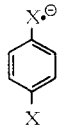
The many anionic redox systems of the Wurster type with oxygen as the end group, *e.g.* most of the vat dyes, are sufficiently characterized by eq. (m). Heterocycles such as indigo [SEM: *(37)*] also form two-stage redox systems of type B[53]. Even silicon *(38)*[54a] and phosphorus *(39)*[54b] may serve as end groups.

B, n = 2



(37)

RED, SEM, OX

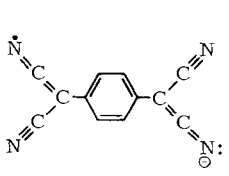


(38), X = $Si(CH_3)_3$ *(39)*, X = $P(CH_3)_2$

OX, SEM OX, SEM

The radical anions *(40)*[55], *(41)*[57], and *(42)*[58] can be interpreted as derivatives of the tetracyanoethylene radical anion *(26)* with inserted aromatic groups. Because of the interesting possible applications of *(40)* (cf. Section 4), the influence of numerous ring substituents in this system has been studied[56].

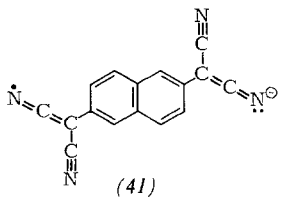
B, n = 3



(40)

RED, SEM

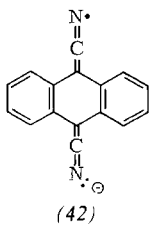
B, n = 4



(41)

RED, SEM

B, n = 2

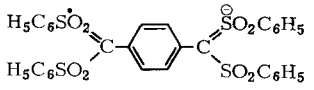


(42)

RED, SEM

Even the sulfonyl group can serve as an end group for such two-stage redox systems, as shown by *(43)*; in this system the d-orbitals of the sulfur are presumably also involved[59].

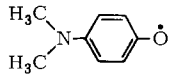
B, n = 3



(43)
RED, SEM, OX

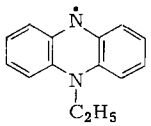
4-Aminophenoxide and its derivatives can be ascribed to type C (RED); extensive ESR investigations have been carried out on the relevant neutral radicals such as *(44)*[60]. The long-known phenazyl radical *(45)* also belongs to this system[61].

C, n = 2



(44)

C, n = 1



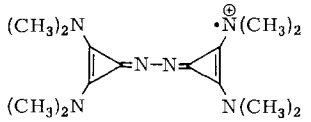
(45)

2.3.2. Two-Stage Redox Systems of the Inverse Wurster Type

The designation "inverse Wurster-type" is used for two-stage redox systems whose end-groups are located outside a cyclic π-system that exhibits aromatic character in the oxidized form.

Cyclopropenylium ions as aromatic groups formally fulfil the aforementioned conditions. In particular, substitution in the three-membered rings with $-N(CH_3)_2-$ groups permitted preparation of the very stable radical cation *(46)*[62,63]. The conditions are less favorable for the radical cation *(47)*, in which the three-membered rings function as end groups, but under carefully controlled conditions *(47)* can be obtained by a reversible reduction of the corresponding dication[64].

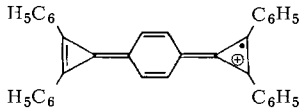
A, n = 4



(46)

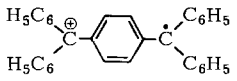
RED, SEM, OX

A, n = 3



(47)

SEM, OX



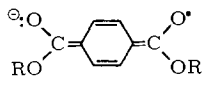
(48)

RED, SEM

(48) is another radical cation[30,65] that is derived from a hydrocarbon.

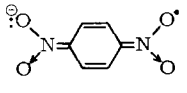
The two-stage cationic redox systems of general type A are complemented by anionic systems of type B, for which *(49)*[38,66] and *(50)*[67] could serve as characteristic examples.

B, n = 3



(49)

OX, SEM

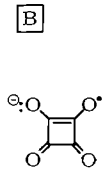


(50)

OX, SEM

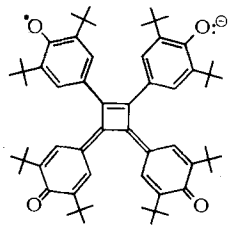
If cyclobutadiene dications substituted by donor groups constitute the cyclic π-systems, then *e.g.* the squaric acid dianion can be regarded as a Wurster-type two-stage redox system; the corresponding radical anion *(51)* can be detected polarographically[68]. As a phenylog of *(51)*, *(52)* represents a very stable radical anion in a two-stage redox system[69]. Replacement of the oxygen in *(51)* by nitrogen as in *(53)* leads to a radical anion of unusually high stability ($K = 2 \times 10^{15}$!)[70].

B



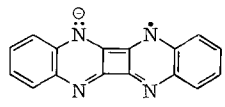
(51)

SEM, RED



(52)

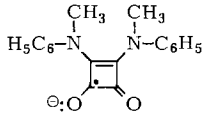
OX, SEM, RED



(53)

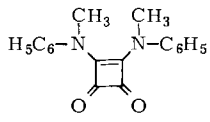
OX, SEM, RED

Closely related to the general redox types considered so far are the 1,2- and 1,3-squaric acid diamides. Some of these neutral compounds can be both reduced in one stage and also oxidized in one stage, as shown in the examples *(54)*/*(55)* and *(56)*/*(57)*[70,71].

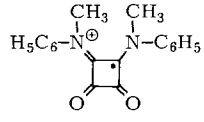


(54)

$SEM^{\ominus}$

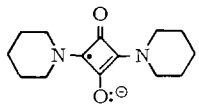


$(54)_{OX} \equiv (55)_{RED}$



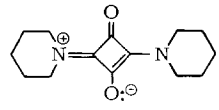
(55)

$SEM^{\oplus}$

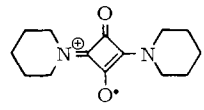


(56)

$SEM^{\ominus}$



$(56)_{OX} \equiv (57)_{RED}$



(57)

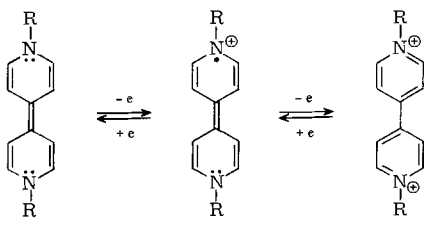
$SEM^{\oplus}$

2.3.3. Two-Stage Redox Systems of the Weitz type

The designation "Weitz type" refers to two-stage redox systems in which the end groups form parts of a cyclic π-system that exhibits aromatic character in the oxidized form.

Weitz was the first to recognize the long-disputed reduction of bisquaternary 4,4'-bipyridinium salts $(58)_{OX}$ ("viologens") to violet solutions which become decolorized again on further reduction[72,11b] as two-stage one-electron transfer. These relationships are shown in equation (u).

A, n = 3



$(58)_{RED}$ $(58)_{SEM}$ $(58)_{OX}$

(u)

The recent systematic investigations of the Weitz type call for a separate progress report[73] and only a few examples will be presented here. The radical cations *(59)*—*(62)*[74-77] and the radical anion *(63)*[78] have been singled out as the simplest systems of this type.

A, n = 1



B, n = 1

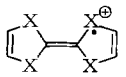


(59), X = NH; *(60)*, X = NC_2H_5; *(61)*, X = O; *(62)*, X = S

(63)

The stable radical cations *(64)* and *(65)* derived from tetrathio-[79,80] and tetraselenofulvalene[81] (cf. Section 4) are of wide interest. The vinylog *(66)* has also been recently synthesized[82].

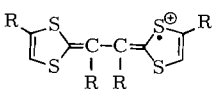
A, n = 1



(64), X = S; *(65)*, X = Se

RED, SEM

A, n = 2

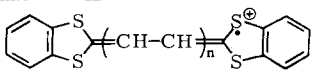


(66)

RED, SEM

The benzo derivatives *(67)*[80] and *(68)*[83] also form stable radical cations.

A, n = 1,2

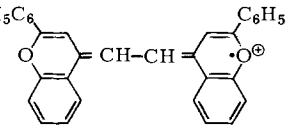


(67), n = 0; *(68)*, n = 1

RED, SEM

Vinylogous bisflavylium salts also exist as two-stage redox systems; for example, *(69)* as a deep blue radical cation[84].

A, n = 4

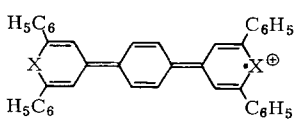


(69)

RED, SEM, OX

A special position is occupied by the Weitz systems containing inserted *p*-phenylene groups, since these achieve aromaticity either in the OX stage [*(70)*[85], *(71)*[85], *(72)*[86]] or in the RED stage [*(73)*, *(74)*, *(75)*[86]] depending on the length of the system.

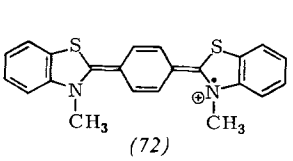
A, n = 5



(70), X = N–CH_3
(71), X = O

RED, SEM, OX

A, n = 3

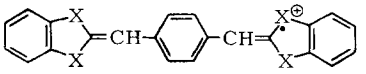


(72)

RED, SEM, OX

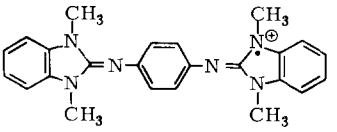
Accordingly, *(70)*—*(72)* can be rather easily oxidized, whereas *(73)*—*(75)* can be easily reduced. The thia derivative *(76)* has to be included in this series[86].

A, n = 4



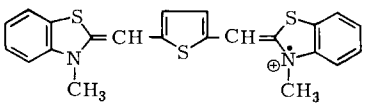
(73), X = N–CH_3
(74), X = S

RED, SEM, OX



(75)

RED, SEM, OX

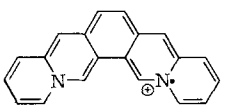


(76)

RED, SEM, OX

Finally, heteroarenes with bridgehead N atoms, such as *(77)*, also belong to the Weitz type[87].

A

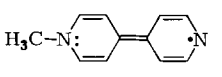


(77)

RED, SEM, OX

In some cases the general redox-type C with a neutral radical as the central member has also been realized as a Weitz type; *(78)* is an example[88]; as a result of the lower symmetry, both the thermodynamic and the kinetic stability of these radicals are greatly reduced in comparison with *(58)*.

C, n = 3



(78)

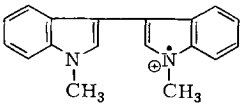
RED, SEM, OX

2.3.4. Two-Stage Redox Systems of the Inverse Weitz Type

The term "inverse Weitz type" denotes redox systems whose end groups are (a) part of a cyclic π-system that (b) exhibits aromatic character in the reduced form.

This type was earlier called a "hybrid type" because the structural characteristic of the Weitz type (a) was bound up with that of the Wurster type (b). Derivatives of indole and indazole should be specially mentioned as examples. Thus, 1,1'-dimethyl-3,3'-biindole forms the stable radical cation *(79)*[89], and four vinylogs of this cation are now also known[89]. Corresponding remarks apply to the aza-vinylogous indazole derivative *(80)*.

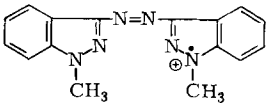
A, n = 2



(79)

RED, SEM, OX

A, n = 3

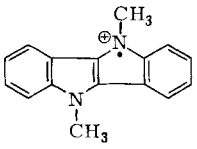


(80)

RED, SEM, OX

The annelated indole rings in *N,N'*-dimethylindoloindole have the same structural features, so that it proved possible to obtain the very stable radical cation *(81)*[90]. The related radical cation *(82)* could be assigned to the Wurster type[90].

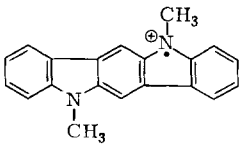
A, n = 1



(81)

RED, SEM, OX

A, n = 2

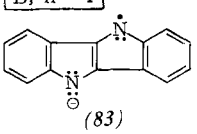


(82)

RED, SEM, OX

The general type B has been verified in this field, as shown by the stable radical anions *(83)*[90] and *(84)*[91].

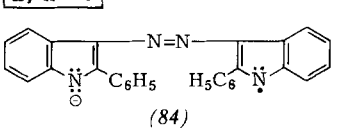
B, n = 1



(83)

RED, SEM, OX

B, n = 3



(84)

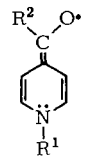
RED, SEM, OX

2.3.5. Two-Stage Redox Systems of Semi-Weitz Type

The semi-Weitz type denotes two-stage redox systems in which one end group is part of a cyclic π-system that exhibits aromatic character in the oxidized form.

This structural type appears to have been verified only as the general redox type C. The neutral radicals are derived mainly from 4-substituted pyridines [*(85)*—*(87)*][16,92a]. *(87)* is green.

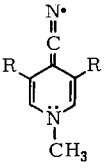
C



(85), $R^1 = R^2 = CH_3$

(86), $R^1 = CH_3$, $R^2 = OCH_3$

(87), $R^1 = Si(CH_3)_3$, $R^2 = OCH_3$



(88), R = H

(89), R = CH_3

Whereas *(86)* is a blue, distillable solid, only tetrahydrofuran solutions of *(88)* are stable for a few days. In acetonitrile *(88)* dimerizes readily with loss of the cyano groups, yielding the Weitz system *(58)*. *(89)* is stabilized by the methyl groups in the *o*-positions[92b].

3. Reactions of Two-Stage Redox Systems

Because of the extremely rapid electron transfer[9,73,93], all three forms of the redox system *(90)* [cf. eq. (o)] are available for reactions, even if one or two of the oxidation stages are present in the equilibrium mixture only in minimal amounts.

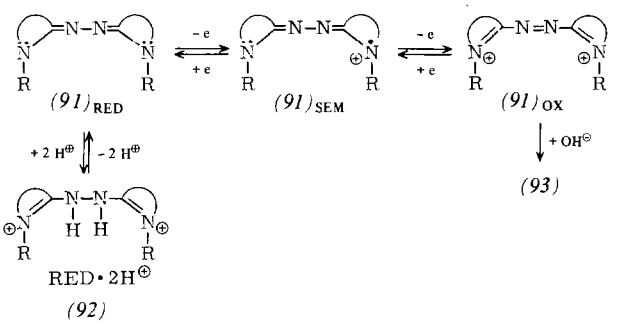


RED[a]		SEM		OX^{a-2}
(90)		*(90)*		*(90)*
Reacts with electrophiles (protons)		Assumes an intermediate position		Reacts with nucleophiles (bases)

Since the RED form contains non-bonded electron pairs, it is in principle sensitive to electrophiles (protons!), this property being more pronounced the more negative charges are carried by the RED form and the more negative is the RED/SEM potential.

Correspondingly the OX form, which has two electrons fewer at its disposal, should in principle be able to react with nucleophiles (bases!) and this the more readily the more positive charges are carried by the OX form and the more positive is the SEM/OX potential.

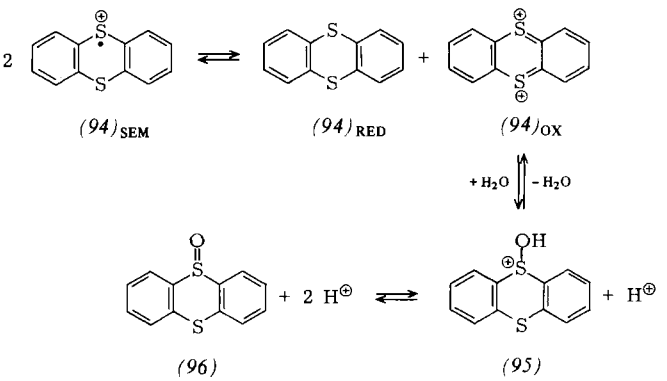
The redox system *(91)* may serve as an example. In accord with the semiquinone formation constant $K = 10^6$—10^{10} [see eq. (t)], the solutions of the violet to blue radical cations $(91)_{SEM}$ contain only traces of $(91)_{RED}$ and $(91)_{OX}$. Yet the color due to the radical disappears immediately on the addition of acid: 50% of RED·$2H^{\oplus}$ *(92)* and 50% of $(91)_{OX}$ are formed. The color change is completely reversible on neutralization, and cannot be visually distinguished from that of an acid-base indicator[94]. Equally, by attack on $(91)_{OX}$, hydroxide ions remove the radical cation $(91)_{SEM}$ from the equilibrium mixture, giving rise to 50% of $(91)_{RED}$ and undefined decomposition products *(93)* of $(91)_{OX}$[95].



$(91)_{RED}$ $(91)_{SEM}$ $(91)_{OX}$ *(93)*

RED·$2H^{\oplus}$ *(92)*

Numerous experiments with the thianthrene radical cation (added as solid) have been particularly informative[48]. The strongly positive potentials $E_1 = 1.23$ V and $E_2 = 1.74$ V ($K = 4.4 \times 10^8$)[96] already show that $(94)_{SEM}$, and particularly $(94)_{OX}$, must be very sensitive to nucleophiles. $(94)_{SEM}$ is stable only in highly purified, non-basic solvents[97]; the dicat-



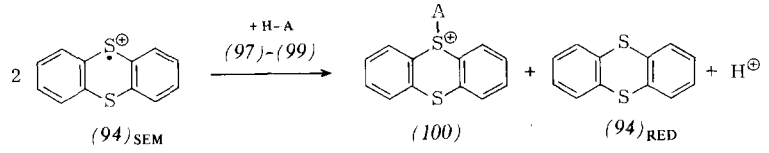
$(94)_{SEM}$ $(94)_{RED}$ $(94)_{OX}$

(96) *(95)*

ion $(94)_{OX}$ is stable only in 100% sulfuric acid[98]. On contact with water it passes, *via* *(95)*, into thianthrene 5-oxide *(96)*, from which $(94)_{OX}$ is formed by the reverse reaction. As a result, $(94)_{SEM}$ can be obtained smoothly from equimolar amounts of $(94)_{RED}$ and *(96)* by means of strong acids[99]. $(94)_{SEM}$ also reacts with water, yielding 50% of $(94)_{RED}$ and 50% of *(96)*, the kinetics showing that the nucleophile attacks $(94)_{OX}$[100].

Furthermore, the *C*- and *N*-nucleophiles *(97)*[101,102], *(98)*[103], and *(99)*[104,105] combine with the thianthrene-sulfur, thus affording *(100)*. Since no radical product is formed,

the stoichiometry shown in the reaction scheme applies throughout.

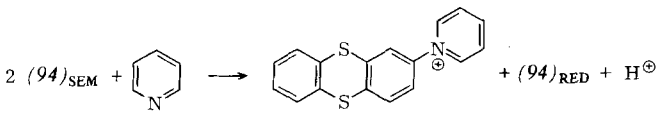


(94)$_{SEM}$ *(100)* *(94)*$_{RED}$

(97), H–A = H–CH(R′)–C(=O)–R; *(98)*, H–A = H–C$_6$H$_4$–R (R = OCH_3, OH, NH_2);

(99), H–A = H–NHC$(CH_3)_3$

One plausible exception is provided by pyridine, which reacts by the same stoichiometry to yield *(101)*[106].



(101)

The mechanism must be carefully investigated in each individual case: whereas *(101)* is very probably formed by way of *(94)*$_{OX}$[106], the nucleophile *(98)* attacks *(94)*$_{SEM}$ directly[107].

4. Applications of Two-Stage Redox Systems

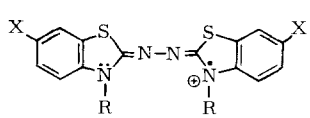
The examples given in this review show clearly how varied are the developments based on the general structural principle presented in equations (p) to (r). Systems are thus accessible that differ very strongly in respect of the position of the redox potentials E_1 and E_2, the thermodynamic and kinetic stabilities of the RED, SEM, and OX partners, the UV/VIS absorption of the RED, SEM, and OX partners, the sensitivity to acids and bases[108], and the solubility in different solvents.

Further, taking into account that the SEM form always shows absorption at by far the longest wavelength and that electron transfer is diffusion-controlled[9,108], then these redox systems can be considered for redox indicators, as electron donors and acceptors, as catalysts for electron transfers, as light-sensitive systems, and as electronic conductors.

Of these possible applications some have already acquired industrial importance and others seem highly promising.

4.1. Redox Indicators

In cerimetric oxidations of metal ions and complex ions the pale yellow form *(103)*$_{RED}$ is a good reversible redox indicator[109]. The usual indication of the equivalence point in bromometric methods, involving an oxidative destruction of an azo dye, could advantageously be replaced by the reversible formation of the radical ions *(102)* or *(103)*, *e.g.* in the titration of ascorbic acid[110].



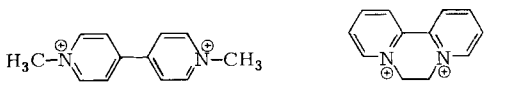
(102), X = H
(103), X = $SO_3^{\ominus}$

R = CH_3, C_2H_5

The application of such redox systems in (automated) biochemical analyses could be profitable.

4.2. Herbicides

The herbicides Paraquat® *(104)* and Diquat® *(105)*[111], which act on the green parts of all plants during illumination, have already gained extensive use. They remove the primary energy for photosynthesis from the plants, in that they trap

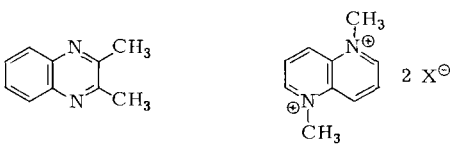


(104) 2 $X^{\ominus}$ *(105)* 2 $X^{\ominus}$

electrons and thus prevent photophosphorylation[112]. Their action, *inter alia*, is restricted to a narrow potential region ($E_2 = -0.3$ to 0.5 V/saturated calomel electrode)[113]. Compounds of this type are also used in studies of photosynthesis[114].

4.3. Redox Catalysts for Photographic Purposes

Redox catalysts are used in photography mainly for activation of developers. Thus, the silver halide reduction in the usual photographic process can be accelerated by Weitz systems such as *(104)* and *(105)*[115]. Furthermore, not only the long-known quinozalines[116] such as *(106)* (type B) but also Weitz systems such as *(107)*[117] (type A) are suitable redox catalysts for the oxidation of elemental silver in silver color-bleaching processes.



(106) *(107)*

Moreover, compounds that effect sensitization[118] or desensitization[119] of photographic material are activated by Weitz-type redox catalysts, *e.g.* *(104)* and *(105)*.

4.4. Image Production by Two-Stage Redox Systems

4.4.1. Photographic Systems

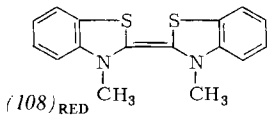
In the manner known for some time for primary and secondary alcohols[120], a bipyridyl salt *(58)*$_{OX}$ of the Weitz type, dissolved in a cross-linked polyvinyl alcohol layer, is reduced by the alcohol on irradiation ($\lambda < 360$ nm), thus affording the radical cation *(58)*$_{SEM}$ [eq. (v)]. On subsequent treatment with a silver salt solution, *(58)*$_{SEM}$ reduces the silver ions to metallic silver [eq. (w)], which serves as a nucleus for

subsequent physical development of the photographic negative[121].

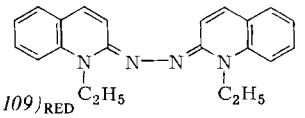
$$2\ (58)^{2\oplus}_{OX} + \text{>C(H)OH} \xrightarrow{h\nu} 2\ H^{\oplus} + \text{>C=O} + 2\ (58)^{\oplus}_{SEM} \qquad (v)$$

$$(58)^{\oplus}_{SEM} + Ag^{\oplus} \longrightarrow (58)^{2\oplus}_{OX} + Ag \qquad (w)$$

A photothermographic material that gives a positive image directly can be made from silver salts of long-chain carboxylic



$(108)_{RED}$



$(109)_{RED}$

$$(108)/(109)_{RED} + Ag^{\oplus} \longrightarrow Ag + (108)/(109)^{\oplus}_{SEM} \qquad (x)$$

$$(108)/(109)_{RED} + (RCBr_3) \xrightarrow{h\nu} R\dot{C}Br_2 + (108)/(109)^{\oplus}_{SEM}\ Br^{\ominus} \qquad (y)$$

(110)

acids and Weitz systems with relatively high potential in the RED form, *e.g.* *(108)* or *(109)*, for nucleation. Upon heating these compounds produce silver nuclei according to eq. (x), which catalyze the reduction of the silver salts in their neighborhood. When exposed to light, the radical sources of type *(110)* that are present convert the nucleating agents $(108)/(109)_{RED}$ into the SEM form in accord with eq. (y), and in that form these are no longer effective as reducing agents: thus a positive picture is formed[122].

4.4.2. Electro-optical Systems

Transformation of electrical information into an optical image and later erasure thereof is made possible by the use of electrode-plates, of which one is transparent. Between them there is a solution of *e.g.* a bipyridinium salt $(58)_{OX}$. On

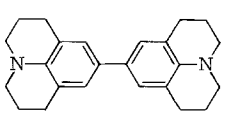
$$(58)^{2\oplus}_{OX}\ 2\ X^{\ominus} \underset{-e}{\overset{+e}{\rightleftharpoons}} (58)^{\oplus}_{SEM}\ X^{\ominus} + X^{\ominus} \qquad (z)$$

colorless blue

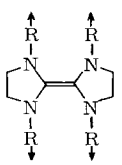
application of a direct current a blue precipitate of the considerably less soluble radical salt $(58)^{\oplus}_{SEM}X^{\ominus}$ is formed on the cathode within ≤ 10 ms, provided that the *N*-alkyl groups in *(58)* are sufficiently long. The image is instantly erased by reversing the polarity [eq. (z)][123].

4.5. Organic Semiconductors, Organic Metals[124]

Applications in this field, which is in the process of very rapid development, may gain immense importance in the future. Two directions of research stand out: a) Weitz systems are used as salts of the OX form, *e.g.* $(69)_{OX}$ and $(71)_{OX}$[125], or Wurster systems in the RED form, *e.g.* $(111)_{RED}$[125]. These are embedded in a polymer layer. A similar redox system of type A can also be used as a polymer[125], *e.g.* the polymer $(112)_{RED}$ made *via* bifunctional arenes[126]. In this way semiconductor films with an electrical conductivity of $\approx 10^{-2}$ to $10^{14}\ \Omega^{-1}\ cm^{-1}$ can be produced, which could be used for thermistors, photosemiconductors, and solar batteries[127]. In particular, a minimal doping of the OX or RED form with the SEM radical ion produces a strong increase of the conductivity[128]. Such films are therefore suitable for xerographic purposes[125, 126, 4].



(111)



(112), R = Aryl

b) In the second case, deeply colored salts are produced from radical cations and radical anions. Of these, the combination of $SEM^{\oplus}$ from tetrathio- or tetraselenofulvalene *(64)* or *(65)* with the $SEM^{\ominus}$ from tetracyanoquinodimethane *(40)* holds a predominant position. With single crystals at room-temperature a conductivity of $10^{3}\ \Omega^{-1}\ cm^{-1}$ has been achieved; hence the name "organic metals" has been coined for such compounds[129]. Below 60 K superconductivity even seems to appear. The reactants must fulfil definite requirements in respect of the redox potential, polarizability, size, *etc.*, and above all the two oppositely charged radical ions must be anchored columnwise next to one another in a completely defect-free lattice. The extremely high demands made thereby on the purity of all the substances used are at present the main obstacle to the development of this new class of electronic conductors.

5. Outlook

An almost inconceivable variety of multistage redox systems arises on the basis of the general structural principle described. By their use the electrochemical, electrical, and spectral properties and the behavior toward solvents and substrates can be studied in dependence of the molecular and the crystal structure (cf. [130]). The generalizations and rules thus uncovered should pave the way to tailor-made molecules whose redox character depends solely on electron transfer.

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Physical and Chemical Properties of Dissolved Electrons (Excess Electrons)

By Ulrich Schindewolf[*]

Electrons produced in a gaseous, liquid, or solid solvent are called dissolved electrons or excess electrons. These excess electrons can exist as quasi-free particles of high mobility in a delocalized state, comparable with electrons in a metal; or as bound particles of low mobility they can be localized within narrow limits—in a solvent cavity formed by repulsive forces. Localized electrons can also be solvated like normal ions. Characteristically, such solvated electrons exhibit broad and extensive absorption spectra in the visible to near infrared spectral range. The localized and delocalized states of the excess electrons can be in equilibrium with each other, such that a continuous transition of the properties between the limiting extremes can be observed. The reactions of the excess electrons with suitable acceptors (substrates) are initiated by an attachment-detachment equilibrium $A+e^- \rightleftharpoons A^-$ which is followed by further chemical rearrangements. The rate constants of these reactions vary by more than 15 powers of ten depending on the substrates and the solvents. Most of the properties of excess electrons in solution can be interpreted by means of a model which is easily understandable but quantitatively evaluated only with considerable effort.

1. Introduction

The Irish physicist *O. J. Stone* coined the expression "electron" for the unit of electrical charge, after *H. v. Helmholtz*—on the basis of *Faraday*'s investigations on electrolysis—had postulated that electricity is subdivided into very small particles which behave like atoms of electricity. The electron was identified around the turn of the century by proving that the negative particles produced on ionization of air with α- or X-rays, or emitted by β-decay, by photoemission (photoelectric effect), or by the thermoelectric effect, all have identical charge and identical mass. The electrons formed by any of these processes in a vacuum or in highly rarified gases have free mobility (discounting scattering effects). They are, however, scavenged by recombination or reaction with individual molecules (*e.g.* O_2), *i.e.* they have a short lifetime.

On the other hand, electrons produced in a dense phase (gaseous, liquid, or solid solvent) can be stabilized by interaction with the solvent before they are caught in an unoccupied orbital of a single atom or molecule, *i.e.* before they undergo chemical reaction. Depending on the nature of the interaction—which is defined by the system, its density, and temperature—the electron can occupy several states partly in equilibrium with each other. At one end of the scale we have quasi-free electrons of high mobility, comparable with metallic electrons. They are unbound or delocalized, *i.e.* their wave functions, the square of which describes their density, have a wide spatial distribution. At the other end of the scale we have localized electrons of low mobility bound to several solvent molecules (but not occupying any well-defined orbital), such that their wave functions extend only over a few solvent molecules. An extreme of the localized or bound electron state is the solvated state, which occurs in polar solvents, where the electron is trapped in a solvent sphere in a similar way to conventional ions.

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Electrons stabilized in any medium by suitable interactions and not bound to single atoms or molecules are called excess electrons (review literature, symposium proceedings[1-13]). Since these electrons are always in a solvent system, we shall also refer to them as dissolved electrons. In accordance with our definition, the mobile electrons of a metallic or semiconducting system can also be classified as excess electrons.

In nonmetallic systems, the excess electrons are unstable from the thermodynamic point of view: they are continuously undergoing recombination or reaction with the solvent or dissolved impurities. They therefore have a limited lifetime which can vary between 10^{-15} s and several months, depending on the system and its state.

Excess electrons can be generated in most systems by any radiation or photochemical reaction which leads to ionization of the solvent[14], *e.g.*

$$H_2O \xrightarrow{\alpha, \beta, \gamma} H_2O^+ + e^- \quad (1)$$

or of dissolved species[15], *e.g.*

$$I^- \xrightarrow{h\nu} I^\bullet + e^- \quad (2)$$

It follows that the reactions of excess electrons might play an important role in all radiation and photochemical processes; in particular, excess electrons might participate in biological radiation damage and in photosynthesis.

Electrical discharges also produce excess electrons, the mobility and lifetime of which determine the quality of an insulator. Sparking and arcing, *e.g.* in high-voltage switches, can be prevented in an atmosphere which contains components (*e.g.* sulfur hexafluoride) that react rapidly with excess electrons.

Forced ionization as described by eq. (1) or (2) leads to excess electron concentrations up to 10^{-5} mol l^{-1}. However, on dissolution in some polar solvents (*e.g.* ammonia) alkali and alkaline earth metals spontaneously dissociate into excess electrons and positive ions:

$$Na \rightleftarrows Na^+ + e^- \quad (3)$$

giving excess electron concentrations of up to 5 mol l^{-1}. In this system, which has been known for more than 100 years[16], the transition from the nonmetallic to the metallic state *via* a semiconducting state can be accomplished[17] by variation of the excess electron concentration:

$$e_l^- \rightleftarrows e_f^- \quad (4)$$

(localized, subscript l, delocalized or quasi-free, f). This is of great importance for the development of semiconductors[18].

The metal-ammonia solutions are metastable, *i.e.* they decay slowly according to

$$e^- + NH_3 \rightleftarrows {}^1/_2 H_2 + NH_2^- \quad (5)$$

until equilibrium is reached[19], at which point the solvated electrons can be detected very conveniently. An industrial-scale process for the production of heavy water by isotope exchange between hydrogen and liquid ammonia, with dissolved potassium amide as catalyst[20], is performed under conditions in which excess electrons are produced in the reverse reaction (5). Their highly corrosive action upon pump seals *etc.* must be taken into consideration during the planning and construction of heavy water plants.

Metal-ammonia solutions often are used for reduction of organic compounds (Birch reaction[21])

$$e^- + A \rightleftarrows A^- \quad (6)$$
$$A^- + HX \rightarrow AH + X^- \quad (7)$$

The intermediate radical anion formed by electron attachment is protonated in a second step (hydrogenation). The radical anions of almost all aromatic molecules are formed conveniently [according to reaction (6)] in metal-ammonia solutions[22] and in metal-ether solutions[23] (*e.g.* tetrahydrofuran, dimethoxyethane). In ethers and in amines (*e.g.* diethylamine) quantitative formation of metal anions is observed[24] ($2e^- + M^+ \rightleftarrows M^-$). Crystalline salts of metal anions can be obtained from these solutions with the aid of cation complexing agents such as crown ethers[24].

Finally, excess electrons are injected from the cathode into the melt during electrolysis of molten metal salts[25]; they reduce the cations to the pure metals.

The above examples show that excess electrons may be formed in many areas of physics, chemistry, biology, and technology, either as desired species or as unwanted interfering particles, and also show that a knowledge of their properties is necessary for the understanding and the control of such processes.

Excess electrons and their reactions are studied by conductivity or light absorption experiments; a time resolution down to a few ps (10^{-12} s)[26, 27] and a limit of detection down to 10^{-11} mol l^{-1}[28] are now feasible. Consequently, the present article examines the electron mobility and light absorption of excess electrons which together provide the basis for a model of excess electrons. This model also permits interpretation of the extreme differences in reactivity of the electrons in different solvents and toward different substrates. In addition to these topics, we shall also mention the nonmetal-metal transition, which is dependent on mutual interactions of excess electrons at high concentrations.

2. Excess Electron Model and Localization Criterion

2.1. Quasi-Free and Localized Electrons

The first two figures demonstrate the statement given before, that the excess electrons can exist in two different states. In Figure 1 the mean electron mobility in gaseous helium at 4.2 K as determined from the drift velocity in an electrical field is plotted as a function of the density of helium[29]. A density

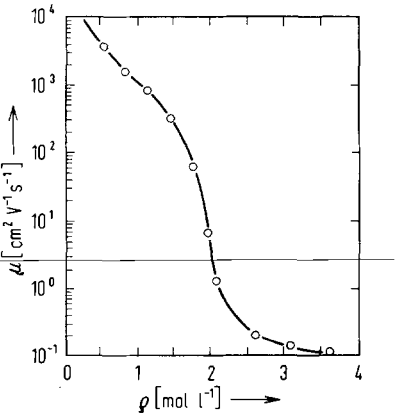


Fig. 1. Mean electron mobility μ in gaseous helium as a function of its density ρ at 4.2 K [29].

decrease in the narrow range between 3 and 1 mol helium per liter (1 to 0.3 bar) results in an increase of mobility by four powers of ten. This increase demonstrates the transition from the localized or bound (but not solvated) state of low mobility to the delocalized or quasi-free state of high mobility (compare Section 3.2).

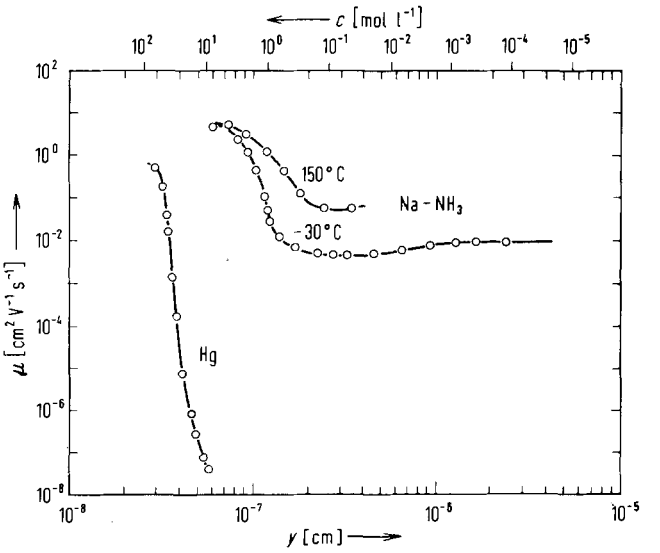


Fig. 2. Mean electron mobility μ in sodium-ammonia solutions at −30 and 150 °C [17, 30] and in supercritical mercury at 1550 °C [31] as a function of the mean distance y between the metal atoms (upper scale metal concentration c).

In Figure 2 the mean electron mobilities in sodium-ammonia solutions[17, 30] and in supercritical mercury[31] measured by

conventional conductometry are shown as functions of the average metal atom distance. At large separations (small concentrations) the mobility of the excess electrons in ammonia is low and independent of concentration, just like that of normal ions in electrolyte solutions: here the electrons are in a solvated, localized state. However, below an average distance of 10 Å (concentration above 1 mol l^{-1}) a mobility increase by three orders of magnitude is again observed, reflecting the transition from the nonmetal to the metal, or in other words, from the localized to the quasi-free electron state (compare Section 4). In supercritical mercury the transition is accompanied by an even larger increase of mean mobility, because in the nonmetallic range the electrons are bound to the nonmobile mercury atoms; they are not excess electrons in the sense of our definition. In the metallic state of both systems the excess electrons have mobilities comparable with those in compact pure metals under normal conditions. However, the mobilities here are still considerably lower than in gaseous helium at low pressure or in some liquid hydrocarbons and some liquified rare gases. Nevertheless, no metallic conductivity can be observed in the latter systems because only very low electron concentrations can be obtained (compare Section 3.2).

2.2. Models

In simplified terms the excess electrons in any medium can occupy two extreme states, the quasi-free, unbound or delocalized state of high mobility and the bound or localized state of low mobility. The distribution between the two states depends on their energy which can be estimated by the formalism of wave mechanics[32-34].

The total energy E of the ground state of the electrons in a solvent is given by the sum of the energy E_e of the electron (kinetic plus potential energy), which follows from the Schrödinger equation with the appropriate boundary conditions, and of the term E_m describing the change in energy of the solvent due to structural changes in the field of the dissolved electrons (rearrangement energy):

$$E = E_e + E_m \tag{8}$$

The quasi-free electron is delocalized over a large volume and hence its charge density is low; consequently the solvent structure will be unaffected and therefore $E_m = 0$.—Polarization of the solvent molecules or atoms (charge shifts within the molecule or atoms) results in an attractive potential, independent of position. Superimposed thereon is the repulsive periodic potential of the solvent molecules, approximated by hard spheres (square well potential) in a periodic arrangement (Fig. 3a). Solution of the Schrödinger equation with this potential leads to the wave function of the excess electrons, the periodic nature of which confirms that the electrons are delocalized over the whole system. It also leads to the energy of the electron E_e, which is identical to the energy V_0 of the lower edge of the conduction band. In highly polarizable liquids the negative potential energy can exceed the positive kinetic energy and therefore the total energy can be negative compared to that of electrons *in vacuo*; *i.e.* energy is released on transferring an electron from vacuum to the solvent.

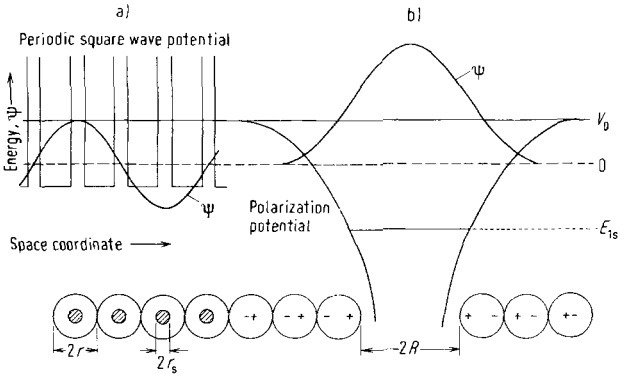


Fig. 3. Simplified representation of energy states and wave functions ψ of a dissolved electron [33]: a) Quasi-free electrons in the periodic square well potential of regularly arranged spherical solvent molecules (the scattering cross section is hatched); the electron is described by a periodic wave function extending over the whole system; the energy of the electron V_0 is identical with the lower edge of the conduction band. b) Localized electron in a solvent cavity, bound by the field of the polarized solvent molecules (indicated by + −). Outside the cavity the wave function asymptotically approaches zero, in the center it assumes a maximum value; the electron has the energy E_{1s} of the 1 s ground state (r radius of solvent molecules, r_s their scattering radius, R cavity radius).

In the localized state the electron is fixed in a small volume with high charge density. Repulsive forces lead to the formation of a solvent cavity ("bubble", "cage") in which the electron is trapped. A decisive role is now played by the attractive polarization potential of the polarized medium which depends upon the spatial coordinates and which is highly negative in polar liquids due to orientational polarization of the solvent molecules. The overall potential interacting with the electron drops steeply inside the cavity; outside the cavity it slowly approaches the V_0 value of the delocalized state (Fig. 3b).

The wave-mechanical treatment results in a wave function which vanishes asymptotically outside the cavity and has a maximum at the center of the cavity, in agreement with the assumption that the electron is fixed therein. In a crude simplification, the localized electron could be described by the model of a particle in a box with a square well potential. But even with the more realistic continuous potential of Figure 3b the positive kinetic energy of the electron increases inversely with the square of the cavity radius R. Again in liquids of high polarization, mainly in those with high orientational polarization, the negative potential energy due to the polarization field might overcompensate the kinetic energy such that the energy of an electron E_e is negative

$$E_e \approx a/R^2 + E_{pot}(R) \tag{9}$$

(in case of the square well potential the constant a is given by Planck's constant h and the electron mass m: $a = 3h^2/8m$).

Formation of the cavity with the accompanying structural changes of the solvent is an energy-consuming process. The rearrangement energy E_m has to be taken into account. It is mainly given by the energy for creating new surface (surface energy $\gamma \times$ cavity surface) and by the pressure volume energy (pressure $p \times$ cavity volume) when forming the cavity:

$$E_m = \gamma 4\pi R^2 + p 4\pi R^3/3 \tag{10}$$

In contrast to E_e of eq. (9), E_m increases with the size of the cavity. The mutually opposing action of the two terms

E_c and E_m in eq. (8) leads to a minimum of the total energy E at a well defined cavity radius, which describes the most stable cavity size of the localized electron.

2.3. Light Absorption

As in a hydrogen atom, the localized electron can also occupy higher energy states while still being localized. The electron can be transferred to these higher states by light absorption in an allowed transition (high transition probability). Consequently the localized electrons absorb light, and their solutions normally display an intense color. The position of the absorption maximum can be estimated, since the energies of the higher localized states (2p, 3p...) can be calculated employing the same formalism as sketched in Section 2.2 for the 1s ground state.

2.4. Results and Localization Criterion

Calculations have been performed using known solvent properties (density, polarizability, static dielectric constant, surface energy, electron scattering cross section). Results are given in Figure 4, in which the total energy of delocalized (V_0) and of localized electrons (ground state 1s, first excited state 2p) in liquid helium, xenon, water, and ammonia are given relative to the energy of the electron at rest *in vacuo*. The energies are partly positive, partly negative; the energy of the localized state can lie above or below that of the delocalized state.

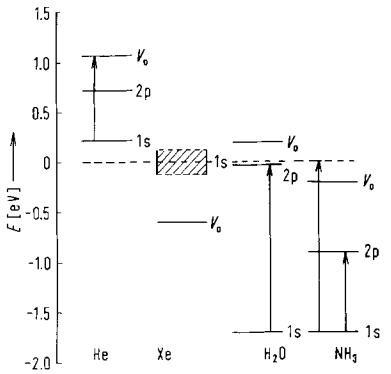


Fig. 4. Energy levels of excess electrons in liquid helium, xenon, water, and ammonia relative to the energy of the resting electron *in vacuo*. V_0 is the energy of the delocalized state, 1s and 2p indicate the energies of the electron in the localized ground state and first excited state. The energy of the 1s state is identical with the solvation energy of the localized electron. Arrows describe observed optical transitions (energy data from [33]).

The localized state is occupied whenever it lies below the delocalized state; the localization criterion is given by

$$E_{(1s)} < V_0 \qquad (11)$$

In all polar liquids with strong orientational polarization (water, alcohols, ethers, ammonia, amines) the localized state has a rather negative energy, the localization criterion is always fulfilled; in these liquids the electron is localized, it is in the solvated state. In nonpolar liquids, which lack orientational polarization, the localized state has a higher energy. It is above that of the delocalized state in liquids of high electron polarizability which have lower V_0 values. (Water and ammonia[33] fit quite well in the series of liquid rare gases in which V_0 decreases with increasing polarizability[36].) Therefore, the localization criterion is no longer obeyed; the excess electrons will stay in the delocalized quasi-free state (liquid heavy rare gases of high polarizability, liquid hydrocarbons, and related compounds with spherical geometry such as methane, tetramethylsilane, neopentane). In weakly polarizable liquified helium or neon, on the other hand, the energy of the delocalized state is still so high that the electrons are localized, although in these solvents the localized state has a positive energy compared to the electron in a vacuum (*i.e.* injection of a vacuum-level electron into liquid helium requires energy, in contrast to the case of ammonia or water, where the solvation energy is released).

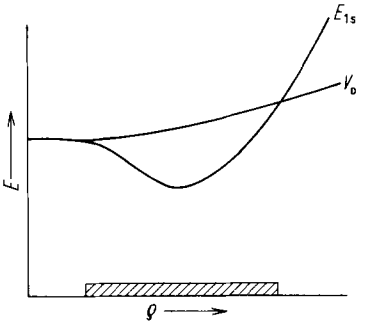


Fig. 5. Dependence of the energy of the quasi-free (V_0) and the localized (E_{1s}) electron state on the density ρ of the solvent (schematic): the electron is localized ($E_{1s} < V_0$) only in the intermediate (hatched) density range.

It follows vividly but not quite correctly from the model presented that a localized electron should be delocalized on increasing *or* decreasing the solvent density (Fig. 5). An increase in density, *e.g.* by applying pressure, leads to a compression of the cavity; this results in an increase of the energy of the localized electron according to eq. (9) such that the localization criterion (11) is no longer fulfilled. With decreasing density on the other hand all interactions will cease more or less abruptly. The electron will assume the properties of a free electron in vacuum.

The calculated energy data of Figure 4 are partly confirmed by experiment: for liquid rare gases and hydrocarbons V_0 values are obtained from the differences of energy thresholds of electron photoemission from a metal into the liquid phase and into vacuum respectively[35, 36]. The energies of the solvated state in water[37, 38] and in ammonia[39, 40] are given by the solvation energies, accessible *via* Born-Haber cycles. The energy differences between the ground and first excited states (1s and 2p) of the solvated electrons follow from the light absorption maxima (see Section 5). The energy difference between the localized and delocalized state in liquid helium is given by the threshold of the inner photoelectric effect[41] (light-induced transfer of an electron from the localized to the delocalized state).

Also theoretical sizes of cavities or "bubbles" in which the electrons are trapped could be confirmed experimentally (effective radius $R \approx 16$ Å in liquid helium from electron mobility applying Stokes' law[42]; ≈ 3.3 Å in liquid ammonia from densities of dilute metal ammonia solutions[43]; < 1.0 Å in water from pressure dependence of electron reaction rates in water[44, 45]).

All data given are of course only average values of a wide distribution function, since thermal density fluctuations of

the solvent lead to fluctuating potentials, cavity sizes, and cavity shapes; they are reflected *e.g.* in the extraordinarily wide absorption spectra of the localized electrons (see Section 5).

3. Electron Mobilities and Diffusion Coefficients

The mobility of electrons μ [$cm^2\ V^{-1}\ s^{-1}$] generated by forced ionization [eq. (1) or (2)] is measured by their drift velocity v in an electric field $\mathfrak{E}$ ($v=\mu\mathfrak{E}$); in a system with time-independent electron concentration (metals, metal solution) the mobility is calculated from the specific conductivity σ ($\sigma=\mu cF$; c metal concentration, F Faraday's constant). The diffusion coefficient D [cm^2/s] follows from the Einstein relation

$$D=\mu kT/e \qquad (12)$$

(k Boltzmann's constant, T temperature, e electronic charge; at 300 K we have $kT/e=2.585\times10^{-2}$ V).

The mobilities vary between the wide limits of 10^4 and $10^{-4}\,cm^2\,V^{-1}\,s^{-1}$ (Fig. 6 and 8; compare Fig. 1, 2) and have led to the distinction between delocalized or quasi-free and localized electrons. We will consider separately solvated electrons in polar solvents and electrons in nonpolar solvents, in which the localized (but not the solvated) or the delocalized states may be occupied with a steady transition between the two.

3.1. Polar Solvents (Dielectric Constant >4)

In all polar solvents so far investigated (alcohols[46], ethers[47], amines[47], water[48], ammonia[17]) the mobility of the solvated electrons is two to fivefold higher than that of normal positive or negative ions[49]. To a first approximation it increases with decreasing viscosity η of the solvent (Fig. 6); however, on going from one solvent to another

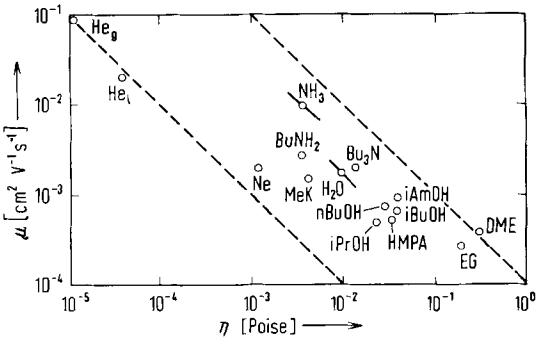


Fig. 6. Relation between mobility μ of localized electrons and viscosity η of the solvent (data from [29, 42, 46—48, 52]); the dotted line on the left follows from Stokes' law with $R=16\times10^{-8}$ cm (He_g, He_l gaseous and liquid helium, respectively; Ne neon, NH_3 ammonia, H_2O water, $BuNH_2$ butylamine, MEK methyl ethyl ketone, Bu_3N tributylamine, iPrOH isopropyl alcohol, iAmOH isoamyl alcohol, iBuOH isobutyl alcohol, nBuOH *n*-butyl alcohol, HMPA hexamethylphosphoramide, EG ethylene glycol, DME dimethoxyethane, all liquid).

Walden's rule ($\mu\sim1/\eta$) is not followed strictly. It cannot be expected to apply exactly because of different solvation structure due to different structure of the solvents or the solvent molecules. In water[50] and ammonia[17], however, the mobility of electrons and that of normal large ions have the same temperature coefficient as the fluidity ($\sim1/\eta$) of the solvent (1.5 to $2.2\times10^{-2}\,K^{-1}$); this proves that the viscosity has a decisive influence on the electron mobility.

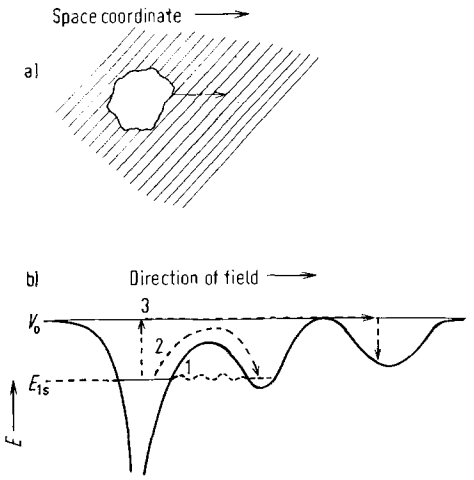


Fig. 7. Illustration of the mobility of a localized electron: a) The electron is pulled with its cavity through the viscous solvent; b) tunnel process (1) or (short range) jump (2) of the electron from its potential well into a neighboring shallow potential trap, formed by random orientation of solvent molecules, or (long range) jump (3) over the conduction band into a distant potential trap.

The higher mobility of electrons as compared to normal ions excludes a normal migration together with their solvation shell (migration of the cavity according to Fig. 7a). The electron, however, can tunnel or jump from its cavity into a neighboring solvent site where the solvent molecules form a shallow potential well by random orientation. Here the electron can be trapped again by forming a stable solvation structure[51] (Fig. 7b).

The approximate inverse proportionality between mobility and viscosity would also be expected for the processes described, for the probability of tunneling or jumping depends upon the probability of forming appropriate potential wells which in turn depends on the mutual mobility of the solvent molecules just as the viscosity does.

3.2. Nonpolar Solvents

Data were collected over a wide temperature interval depending on the range of the liquid states of the respective solvents. Comparison of data should therefore be viewed with some reservation. However, a general trend, is obvious (Fig. 8): the mobilities increase with decreasing energy V_0 of the conduction band.

Group 1: In liquid helium[42] and neon[52] the electrons are localized, because the small polarizability of the liquids leads to high V_0 values ($V_0>E_{1s}$). Consequently the electron mobilities are small ($<10^{-2}\,cm^2\,V^{-1}\,s^{-1}$). They fit roughly in the correlation given by Walden's rule (Fig. 6).

Group 2: In liquid methane[53], argon, krypton, and xenon[54] electrons have high mobilities ($>4\times10^2\,cm^2\,V^{-1}\,s^{-1}$) comparable with those in solid semiconductors. They indicate the quasi-free or delocalized state of the electrons as expected in solvents with low lying conduction band ($V_0<E_{1s}$).

Group 3: In higher hydrocarbons, mobility values between the extremes of localized and delocalized electrons are found.

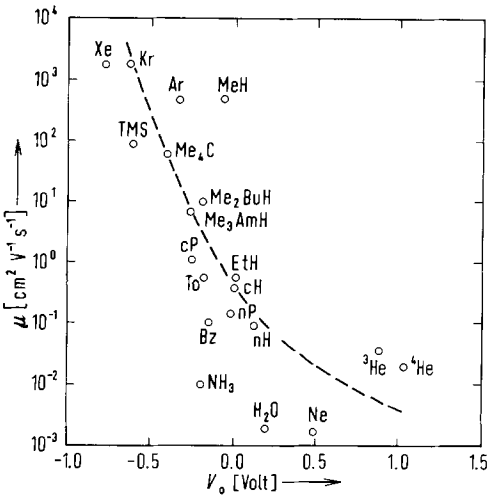


Fig. 8. Electron mobility μ in liquids of varying V_0 values, just below the normal boiling points or at room temperature (μ data from [42, 52—55], V_0 data from [35, 36]; liquified rare gases He, Ne, Ar, Kr, Xe; MeH methane, TMS tetramethylsilane, Me_4C neopentane, Me_2BuH 2,3-dimethylbutane, Me_3AmH 2,2,4-trimethylpentane, cP cyclopentane, cH cyclohexane, EtH ethane, nP *n*-pentane, nH *n*-hexane, To toluene, Bz benzene, NH_3 ammonia, H_2O water).

Some rules can be given[55]: In *n*-alkanes the electron mobility decreases with chain length (methane to dodecane from 4×10^2 to $3 \times 10^{-2}\,cm^2\,V^{-1}\,s^{-1}$). In isomeric hydrocarbons the mobility increases with branching (*e.g.* from 0.09 to $12\,cm^2\,V^{-1}\,s^{-1}$ in the C_6 hydrocarbons). The highest mobilities are found in solvents of spherical molecules such as methane, neopentane, and tetramethylsilane (80 to $400\,cm^2\,V^{-1}\,s^{-1}$).

A normal hydrodynamic movement of the bubble through the viscous medium is assumed for the localized electrons of group 1, which are trapped in a solvent bubble (Fig. 7a). Stokes' law (applied to the mobility) resulted in the large bubble radius in helium[42] and led to the formulation of the cavity model; its theoretical evaluation confirmed this large bubble as the most stable arrangement[33]. Jumping or tunneling is not assumed in this case.

The theory of the quasi-free electrons of metals can be applied to the nonlocalized electrons of group 2[56]. The electrons described as a planar wave are scattered by the molecules or atoms of the liquid phase. The mean free path of the electrons, decisive for their mobility, decreases with temperature due to thermal motion of the scattering centers; this leads to a negative temperature coefficient of the mobility (negative energy of activation, as found *e.g.* in methane[53]).

In the last solvent group with mobilities between the two extremes the quasi-free state of the electrons should lie closely above that of the localized state (V_0 slightly greater than E_{1s}). As in semiconductors, this allows thermal activation of the localized electrons into the quasi-free state of high mobility, from which the electron might jump into a distant potential trap (Fig. 7b). The observed mean mobility is approximated by the product of mobility and relative equilibrium concentration of electrons in the delocalized state[57]. Here again a positive temperature dependence according to Arrhenius is to be expected, because the equilibrium between localized and delocalized state [eq. (4)] is shifted to the right with increasing temperature.

Recent experiments in gaseous helium[58] demonstrate this equilibrium, the density dependence of which can explain the extreme density dependence of the electron mobility of Figure 1.

4. Nonmetal-Metal Transition

The transition from the nonmetal to the metal by transfer of electrons from the localized state of low mobility to the quasi-free state of high mobility is recognized by the steep increase in the electrical conductivity with increasing metal concentration. Examples are metal-ammonia solutions[12, 17, 30] or supercritical mercury[31, 59]. The increase in electron mobility over several powers of ten in a rather narrow concentration range as shown in Figure 2 is characteristic of the transition. However, a metallic state with a specific conductivity above $100\,\Omega^{-1}\,cm^{-1}$ is attained only in solutions with high concentration of the quasi-free electrons ($> 10^{21}\,cm^{-3} \triangleq 1\,mol\,l^{-1}$). Such a concentration is easily obtained in metallic systems by spontaneous ionization. In the nonmetallic systems (Section 3.2) excess electrons can be produced by forced ionization only, *e.g.* by X-rays. This leads to maximal electron concentrations of $10^{16}\,cm^{-3}$. Thus even in xenon, which exhibits the highest electron mobility, a maximal conductivity of only $2\,\Omega^{-1}\,cm^{-1}$ can be achieved, for a very short time only.

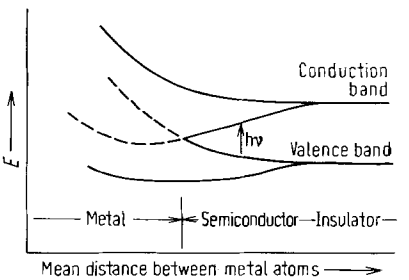


Fig. 9. Illustration of the nonmetal-metal transition by the band model (compare text).

It is easy to give a qualitative interpretation of the concentration dependence of conductivity, *e.g.* of metal-ammonia solutions and of supercritical mercury[60]. Figure 9 represents the energy states of the electrons as a function of the mean distance in terms of a simplified band model. At large distances the electrons are localized in the ammonia solvent cavity or on the mercury atoms. They occupy a discrete level of the valence band (localized state) separated by a wide energy gap from the conduction band (quasi-free state). At smaller distances the electrons undergo mutual interaction which can be described by an overlap of the wave functions; it leads to a broadening of the energy levels which finally form overlapping bands. At large particle distances, *i.e.* large energy differences between the conduction and valence band, the system behaves like an insulator (mercury) or an electrolyte (metal-ammonia solutions). Electrons cannot be promoted from the valence band into the conduction band. At smaller distances, however, the energy gap shrinks and electrons can jump into the conduction band on thermal activation. We then obtain the characteristic of a semiconductor with a positive temperature coefficient of conductivity. Eventually when the bands overlap at smaller distances the electrons can pass into the conduction band without having to overcome an activation barrier and metallic

conduction is observed. In fluid systems the nonmetal-metal transition is smeared out owing to thermal density fluctuations.

Models with a greater degree of sophistication[18,61] give a more detailed but still not exact description of the transition. An almost quantitative description of a series of properties of the metal-ammonia solution was provided by the percolation model[62]. It assumes that the solutions in the transition range are microscopically inhomogeneous, consisting of highly concentrated domains with metallic conduction and dilute domains with electrolytic conduction, each of constant and characteristic concentration. Increase of the overall metal concentration would consequently lead to an increased volume fraction of the metallic domains which finally join to form metallic paths across the solution (Fig. 10).

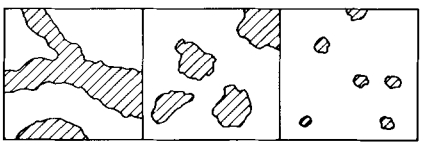


Fig. 10. Illustration of the nonmetal-metal transition according to the percolation theory. Solvent ranges of high metal concentrations are hatched (compare text).

This concept is supported by an opening of the miscibility gap of the solutions at low temperatures[63]; a dilute, nonmetallic and a concentrated, metallic phase are then indeed observed in macroscopic equilibrium. However, it appears doubtful whether the percolation concept is generally applicable to metal-ammonia systems or other systems exhibiting the nonmetal-metal transition.

A common feature of the two models of the transition (compare Fig. 9 and 10) is that the electrons can exist in two equilibrium states—as shown previously for helium[58]. In case of the metal-ammonia solutions a chemical equilibrium

$$e_s^-(iNH_3) \rightleftarrows e_f^- + iNH_3 \qquad (13)$$

could be postulated between solvated electrons (e_s^-) with i ammonia molecules in the solvation shell and quasi-free electrons (e_f^-) with the corresponding number of free ammonia molecules[64]. Addition of electrolytes, *e.g.* sodium iodide, which decreases the concentration of free ammonia by solvation, shifts the equilibrium to the right, *i.e.* favors the metallic state. This follows from the influence of dissolved salts on the miscibility gap.

The thermodynamics of the nonmetal-metal transition of the metal-ammonia solutions are accessible by ammonia vapor pressure measurements[65] or EMF measurements[66] with appropriate electrochemical cells. Figure 11 shows the chemical potential of dissolved sodium relative to solid pure sodium ($\mu_{Na,solid}=0$) plotted as a function of the mole fraction of sodium with temperature as parameter.

The plot demonstrates the nonideal behavior of the solutions, indicating the plateau of the chemical potential in the range of the miscibility gap ($T < -41$ °C), and even at temperatures above it where inhomogeneities according to the percolation concept set in. Further evaluation of the data reveals that the transition to the metallic state is accompanied by a decrease in enthalpy and in entropy and that the miscibility

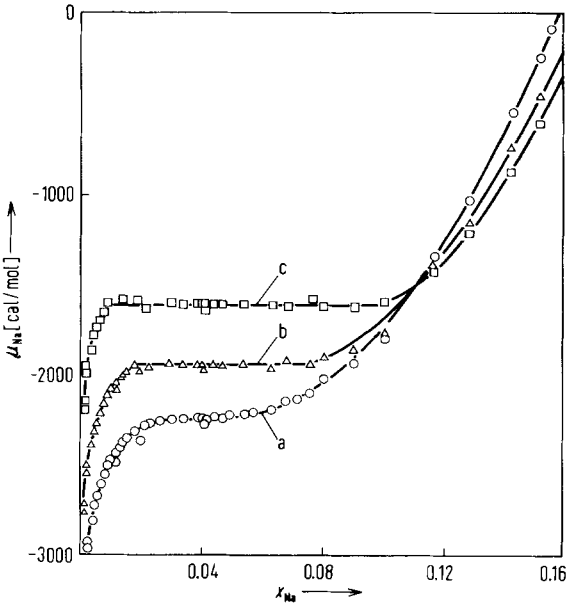


Fig. 11. Concentration dependence of the chemical potential μ of sodium dissolved in ammonia relative to solid sodium ($\mu_{Na,s}=0$; from ammonia vapor pressure [65] and EMF [66] measurements; a -35 °C, b -55 °C, c -75 °C; at -35 °C sodium mole fraction of saturated solution $x_{Na}=0.158$).

gap is a consequence of changes in these thermodynamic functions[18].

5. Absorption of Light

A normal absorption process, in which the energy of the light quantum is transferred to the absorbing species, is not possible with free or quasi-free electrons. Consequently, the quasi-free electrons, such as occur in liquified heavy rare gases or in many hydrocarbons, do not exhibit absorption spectra. A bound or localized electron, however, can interact with a photon, the interaction leading to a higher energy state of the electron. Therefore all solutions containing localized electrons have a strong absorption band (the light absorption is described as a 1s→2p transition (compare Fig. 4) of the electrons for which theory predicts a high transition probability[33]).

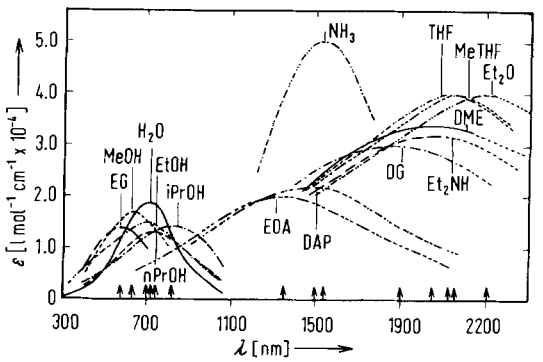


Fig. 12. Absorption spectra of solvated electrons in polar solvents at room temperature [67] (H_2O water, MeOH methyl alcohol, EtOH ethyl alcohol, iPrOH isopropyl alcohol, nPrOH *n*-propylalcohol, EG ethylene glycol, NH_3 ammonia (-33 °C), EDA ethylenediamine, DAP 1,3-diaminopropane, Et_2NH diethylamine, DG diglyme, DME dimethoxyethane, Et_2O diethyl ether, THF tetrahydrofuran, MeTHF methyltetrahydrofuran).

Extensive experimental results have been obtained on the light absorption of localized, and especially solvated electrons

in suitable solvents. The spectra in polar solvents are surveyed[67] in Figure 12, from which the wavelength (λ_{max}) of maximum absorption, the spectral halfwidth (ΔE), and the decadic absorption coefficient (ε) can be read. All spectra are rather broad and lack structure. A relationship clearly exists between λ_{max} and the nature of the solvating group: in solvents containing OH groups (water[68], alcohols from methanol to undecanol[69]) the absorption maximum is located around 700 nm (in branched alcohols λ_{max} is slightly larger than in the corresponding *n*-alcohols[69]), in solvents having NH_2 groups (ammonia[70, 71], amines[72]) between 1200 and 1600 nm, and finally in ethers[72] between 1900 and 2300 nm.

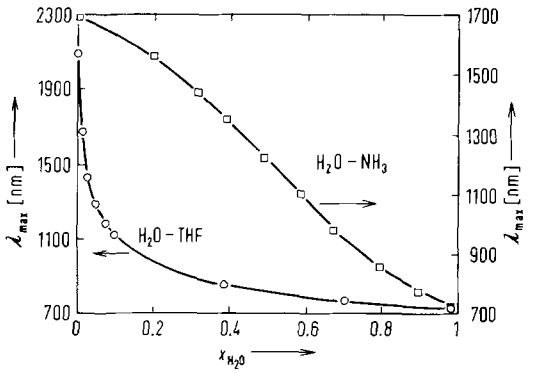


Fig. 13. Wavelength of maximum light absorption λ_{max} of solvated electrons in water-ammonia mixtures [73] and water-tetrahydrofuran mixtures [72] as a function of the mole fraction of x_{H_2O}.

In solvent mixtures the absorption maxima are found between those of the pure components (Fig. 13). In water-ammonia mixtures λ_{max} varies almost linearly with the solvent composition[73], indicating statistical distribution of both water and ammonia between the solvation shell of the electron and the bulk solution. However, in mixtures of solvents with strongly different polarity the more polar solvent molecules are preferentially incorporated in the solvation shell. This follows from the observation that a mere 3% of water in tetrahydrofuran (THF) suffices to shift the absorption maximum to a position halfway between those of the two solvents[72]. Similar effects are observed in alcohol-hydrocarbon mixtures[74].

All attempts to find a simple relation between λ_{max} and typical macroscopic properties of the solvent (dielectric constant, refractive index, surface tension, polarizability, *etc.*) have failed. However, since the size of the solvent cavity in which the electrons are trapped plays a decisive role in determining the energy of the dissolved electrons[33] [compare eq. (9)], the dependence of λ_{max} on the solvent might indicate a variation in cavity size. An evaluation[67] on the basis of the simplified theory leads to cavity radii R of around 0.9 to 1.5 Å in water and alcohols, of 2.5 to 3 Å in ammonia and amines and 3.1 to 4 Å in ethers.

In solid and molten alkali halides a quadratic relation has been confirmed between λ_{max} and a geometric factor d of the solvent (cavity radius $R \sim$ lattice constant d)[75, 25], as is postulated by the simple model of an electron in a box. A red shift of spectra with increasing temperature[68, 71] and blue shift with increasing pressure[44, 71, 76] are interpreted in terms of the cavity model by thermal expansion and compression, respectively, of the cavity.

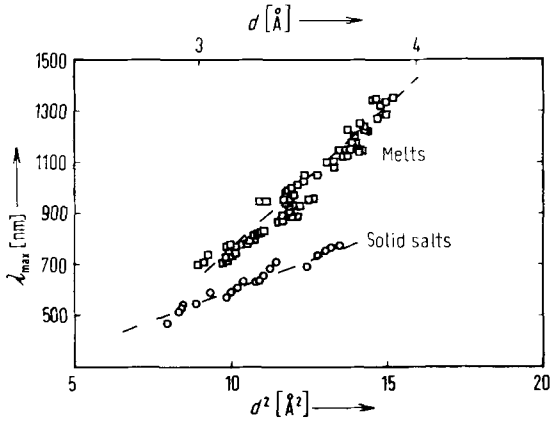


Fig. 14. Quadratic relationship between lattice parameter d and wave length of maximum light absorption λ_{max} of excess electrons in solid (20—400°C [75]) and molten (500—1000°C [25]) pure alkali metal halides and their mixtures (d represents the size of the anionic lattice defects in which the excess electrons are trapped).

The large halfwidth of the spectra can likewise be interpreted with this model. In the disordered liquid phase the thermal motion of the molecules precludes the formation of cavities of uniform size. Instead, the cavity sizes are expected to follow a distribution function with a maximum at the most probable or most stable cavity size. If an electron absorbs only light of a definite wavelength determined by the size of the cavity, the broad absorption spectra indirectly reflect the cavity size distribution function[77]. This view is supported by experiments with alkali metal halides: in the melts the electron spectra are three to four times broader[25] than in the crystal[75] where the electrons are localized in anion vacancies of well defined geometry (F-centers).

Laser experiments with metal-ammonia solutions on a picosecond time scale[27, 78] reveal that the cavity size distribution function is established very quickly. A high intensity laser flash of sharp wavelength in the range of the electron absorption leads to diminished absorption (bleaching) over the *whole* spectrum due to depopulation of the light absorbing state. Selective bleaching of the solution at the wavelength of the laser light is not observed. Immediately after completion of the flash, the spectrum regains its original intensity. This not only proves that the cavity size distribution function is established within a few ps (*i.e.* as fast as molecular reorientations), but also shows that the electrons in the excited state return to the ground state within the same time[79, 80].

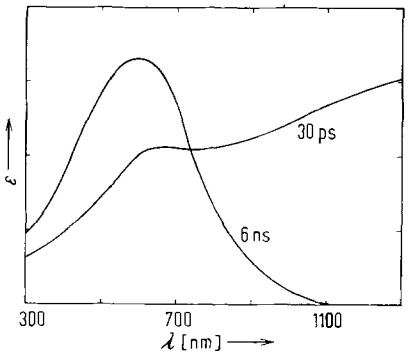


Fig. 15. Absorption spectra of excess electrons in propanol at −12°C, 30 ps and 6 ns after their generation by pulse radiolysis [82] (absorption coefficients in arbitrary units).

In frozen glassy solvents, *e.g.* THF, in which the rate of reorientation of the molecules is decreased by many orders of magnitude, a persistent selective bleaching is observed[81]. This proves the concept that the electrons are trapped in states of various energies or in cavities of various sizes, from which they can be selectively excited, and that here a perturbation of the distribution function is not smoothed out again.

Further picosecond experiments give information on the time scale of the solvation process of electrons[26, 82]. Figure 15 displays the absorption spectrum of electrons in propanol at −12°C, about 30 ps and 6 ns after their generation by a ps-radiolytic pulse. The spectrum is time-dependent. The electron is formed first in a state with an absorption maximum above 1300 nm, which with some delay relaxes to the normal state with an absorption maximum around 600 nm, as shown in Figure 12.

It is assumed that the electron is first trapped in a region of the solvent in which the solvent molecules form a shallow potential well by random orientation. Reorientation of the molecules by the field of the trapped electrons then leads to the stable solvent cavity configuration. The relaxation time of this process increases from 11 to 50 ps in the series of alcohols from methanol to decanol[83], in good agreement with relaxation times for molecular rearrangements in these solvents as determined by dielectric measurements.

Electron solvation is not limited to a condensed solvent phase, but also can occur in the vapor phase. As mentioned in the introduction, however, the solvation process requires a certain minimum density of the solvent. Optical investigations in supercritical ammonia and water vapor, in which the density can be varied at will, reveal the limits: in ammonia[84] just below 0.1 g cm^{-3}, in water[85] around 0.01 g cm^{-3}. The spectra observed in these vapors hardly differ from those in the liquid. At lower densities the solvating interactions are too weak; the electrons remain in a quasi-free delocalized state just as they do in low density helium gas (Fig. 1).

Only little information is available about the absorption spectra of localized electrons in other solvents. In hydrocarbons[86], such as hexane, cyclohexane, methylcyclohexane, and isopentane, the absorption maximum is located at slightly higher wavelengths than in ethers. According to theory, localized electrons in helium should absorb light in the same range[87] (compare Fig. 4).

6. Reaction Rates

The reactions of dissolved electrons in aqueous systems have been investigated most thoroughly: the rate constants of reactions with nearly 700 different substrate molecules have been compiled in tabular form[88]. However, activation energies are given only for 16 of these reactions and hence evaluation of the rate constants—varying between 10^7 and 10^{11} l mol^{-1} s^{-1}—is virtually impossible. Slower reactions ($k < 10^7$ l mol^{-1} s^{-1}) cannot be observed in water because the lifetime of the electrons is limited to 10^{-3} s by reaction with water molecules:

$$e^- + H_2O \rightarrow \tfrac{1}{2}H_2 + OH^- \quad (14)$$

Superimposed upon this is a pseudo-bimolecular reaction

$$2e^- + 2H_2O \rightarrow H_2 + 2OH^- \quad (15)$$

(pseudo-bimolecular rate constant $k = 5 \times 10^9$ l mol^{-1} s^{-1}) which becomes very fast at higher electron concentration. In ammonia the corresponding reaction

$$e^- + NH_3 \rightarrow \tfrac{1}{2}H_2 + NH_2^- \quad (16)$$

is slower by many orders of magnitude [in pure metal-ammonia solutions the lifetime of electrons exceeds several weeks; the pseudo-bimolecular reaction corresponding to eq. (15) has not been observed]. Therefore even extremely slow reactions can be followed in ammonia. In nonpolar solvents, reactions many times faster than those occurring in water have been found. Thus the rate constants of electron reactions in different solvents cover the range from $k < 1$ to about 10^{15} l mol^{-1} s^{-1}. However, the experimental rate constants of a reaction such as

$$e^- + A \rightarrow \text{Products} \quad (17)$$

(A electron acceptor molecule) describe only the overall rate with which the electrons disappear from the solution without revealing any details of a reaction mechanism.

The experimental information available so far shows the electron reaction rates to be strongly dependent on the solvent:

1) *via* its viscosity or other properties which influence the mobility or the rate of diffusion of the electrons
2) *via* its influence on the properties or the reactivity of the electrons and their reaction partners
3) *via* its dielectric constant which is decisive for the Coulomb interaction in reactions with ions
4) *via* its participation in consecutive reactions.

These four points will be illustrated separately with the aid of examples; the sparse experimental data obtained in nonaqueous solvents and solvent mixtures will also be considered.

6.1. Diffusion-Controlled Reactions

We speak of diffusion-controlled reactions whenever the actual reaction step, *i.e.* the chemical transformation of the reactants, is faster than the diffusion processes in which the reactants are brought together or are separated again[89]. For these reactions the bimolecular rate constant k_D is given by the sum of the diffusion coefficients D of the two partners and by the maximum collision distance σ from which the electron can jump or tunnel to the reaction partner

$$k_d = 4\pi N_L D\sigma/1000 \ [\text{l mol}^{-1}\ \text{s}^{-1}] \quad (18)$$

(N_L Loschmidt number). The diffusion coefficient of the substrate can be neglected because it is small compared to that of the fast moving electron. The diffusion coefficients of the electrons follow from their mobilities *via* eq. (12).

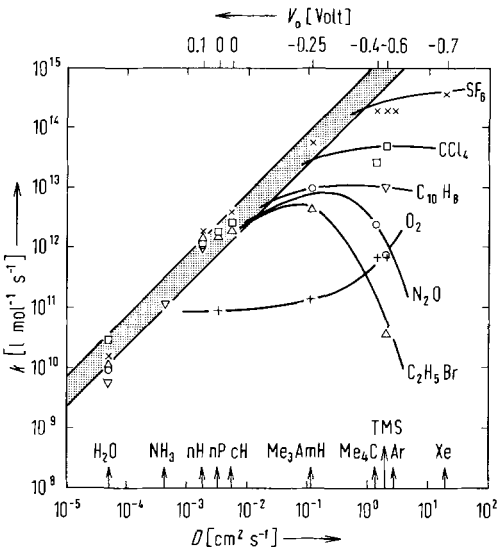


Fig. 16. Relation between rate constant k of some reactions of excess electrons and their diffusion coefficients in several solvents. The reaction partners are given on the right-hand side, the solvents on the abscissa, their V_0-values are indicated at the top of the figure. The hatched area is calculated for diffusion-controlled reactions according to eq. (18) with the collision distance $\sigma = 3 \times 10^{-8}$ to 1×10^{-7} cm (data from [88, 90, 91]; H_2O water, NH_3 ammonia, nH *n*-hexane, nP *n*-pentane, cH cyclohexane, Me_3AmH trimethylpentane, Me_4C neopentane, TMS tetramethylsilane, Ar argon, Xe xenon; $C_{10}H_8$ naphthalene).

In Figure 16 the relation between the rate constant of diffusion-controlled reactions of the electrons and their diffusion coefficient calculated according to eq. (18) with collision distances between 3×10^{-8} and 10^{-7} cm is shown hatched. The experimental rate constants of some selected reactions in a series of solvents are included for sake of comparison[88, 90, 91]. All the reactions with rate constants in the hatched area are diffusion controlled beyond any doubt. Here the individual properties of the solvent, of the reaction partner, and of the electron (localized or quasi-free) are without influence on the reaction rate. The sole decisive factor for the rate is the electron diffusion coefficient.

6.2. Influence of Solvent

In liquids of extremely high electron mobility the proportionality between k_d and D shown in eq. (18) is no longer valid. The rate constants lie below the diffusion-controlled limit (Fig. 16). We have reached the domain in which the actual chemical transformations become rate determining.

This can be stated more precisely. According to the laws of diffusion the electron will pass through the distance σ, from which the electron can be transferred to the reaction partner, in a time

$$\tau_D = \sigma^2/2D \tag{19}$$

In a diffusion-controlled reaction the actual reaction time τ_R in which the electron can be transferred must be smaller than τ_D. Thus, for $\sigma = 5 \times 10^{-8}$ cm and $D = 1$ cm^2 s^{-1}, τ_R should be smaller than 10^{-15} s.

It is obvious that rearrangements of the solvent structure or of the reaction partner to obtain a reactive configuration cannot occur on such a short time scale. Only tunneling would allow such fast processes and there are adequate arguments[7] in support of the assumption that the reactions of excess electrons occur *via* tunneling. But then why are not all electron reactions as fast as diffusion would allow, and why are some reactions up to 10^{15} times slower?

To explain the differences in reactivity of electrons with the same substrate in different solvents or with different substrates in the same solvent we modify the simplified theory of charge transfer reactions (redox reactions, *e.g.* electrode-electrolyte) which is based on the concept of tunneling[92]. Applied to the reactions of dissolved electrons this means that the electron has to tunnel from its state in the solvent to an unoccupied orbital of the acceptor molecule[93, 94]. Since tunneling is very fast the molecular configurations of the system cannot change during electron transfer. This is comparable to electronic excitation of a molecule where the geometric configuration initially also remains unchanged (vertical transition according to the Frank-Condon principle). The resulting negative molecule ion is formed not in its most stable state but in the equilibrium configuration of the neutral molecule, from which it goes to the stable state with dissipation of excess energy. The solvent area in which the electron was trapped will likewise rearrange to its normal state after some time has elapsed, dissipating the rearrangement energy E_m of eq. (10). Thus the reaction enthalpy ΔH will clearly be set free with some delay after the electron transfer.

Since tunneling is possible only between states of identical energy (interpretable on a simplified level as resonance), electron transfer will occur only when the acceptor molecule has a free orbital in the energy range of the free electron. The theory of tunneling rather vividly describes the tunneling probability at a given energy E as the product of three parameters: the tunneling frequency $\nu(E)$ depending on the width and height of the potential barrier, and the two densities of states $D_0^e(E)$ and $D_0^A(E)$ describing the density of occupied (o) energy levels of the dissolved electron (e) and that of the unoccupied (u) levels of the acceptor molecule (A), all three at the energy E. To obtain the overall transition probability we have to integrate over all energies from $-\infty$ to $+\infty$. Apart from constant factors we obtain

$$k \sim \int_{-\infty}^{\infty} \nu(E)\, D_0^e(E)\, D_0^A(E)\, \mathrm{d}E \tag{20}$$

Figure 17 schematically shows the density of states of delocalized electrons described by the sharp V_0 values in *n*-hexane (a), 2,2,4-trimethylpentane (b), and tetramethylsilane (c), as well as the densities of the unoccupied energy states of several acceptor molecules 1 to 3. These follow from electron affinities and the solvation energies of the molecules; they are independent of solvent, at least in hydrocarbons of low dielectric constant.

The $D_0^A(E)$ functions of sulfur hexafluoride and carbon tetrachloride (example 2 of Fig. 17) have broad maxima in the range of V_0 values of all hydrocarbon solvents. The consequences are high reactivities so that the limits of diffusion-controlled reactions are reached in almost all solvents. The $D_0^A(E)$ functions of ethyl bromide and nitrous oxide (example 1 of Fig. 17) are narrower and shifted to higher energies. The rate constant then decreases with decreasing V_0 value (upper scale in Fig. 16). In the case of oxygen (example 3 of Fig.

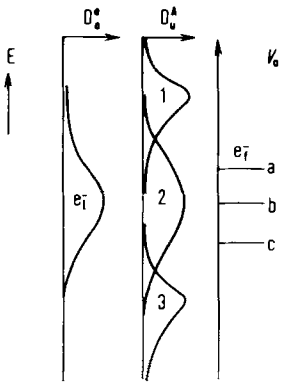


Fig. 17. Schematic representation [93, 94] of the density of state functions of the occupied states $D_o^e(E)$ of a localized electron e_i^- (left) and of a quasi-free electron e_f^- with the sharp energy V_0 in three different solvents (a cyclohexane, b 2,2,4-trimethylpentane, c tetramethylsilane) and of unoccupied states $D_u^A(E)$ of three sorts of acceptor molecules (1 ethyl bromide or nitrous oxide, 2 carbon tetrachloride or sulfur hexafluoride, 3 oxygen).

17) whose distribution function has a maximum at lower energies, the rate constant increases with decreasing V_0.

Decreasing temperature shifts the distribution function of these molecules to lower[93], and the V_0 values to higher energies[35]. Thus decreasing temperature results in better overlap, leading to faster reactions; *i.e.*, a negative activation energy is observed as with nitrous oxide or ethyl bromide in tetramethylsilane. However, other effects might contribute to negative activation energies: equilibrium (4) between localized and delocalized electron states may be shifted in favor of the localized states by a decrease in temperature. The localized state with a lower and wider distribution function can, in certain cases, lead to a better overlap and therefore to higher reaction rates.

These differences are not so sharp in reactions of solvated electrons, because their density functions are wider (Fig. 17, left). Therefore overlap may still occur with molecules whose density of state function is shifted to lower or higher energies. Moreover, since the diffusion-controlled reactions of solvated electrons are considerably slower, differences in tunneling probability or reactivity of different substrate molecules like oxygen, ethyl bromide or sulfur hexafluoride could not be detected at all. In cases of substrates which do not react at all, or if so only slowly, with solvated electrons (methane, nitrogen, or benzene, respectively), we may always assume that the unoccupied orbitals are too high (molecule 1 in Fig. 17).

Without going into details, one other experimental result concerning kinetics in polar solvents will be mentioned. Electrons generated by any energy consuming process, *e.g.* radiolysis, are initially formed in a quasi-free or in a weakly localized state of high energy before they are transformed, on a ps-time scale, into the stable solvated state (compare Fig. 15). In accord with their higher energy, quasi-free electrons will react faster with substrates of higher-lying distribution function (*e.g.* acetone, case 1 of Fig. 17) and slower with those of lower-lying distribution function (H^+ ions, case 3 of Fig. 17) than do solvated electrons. This explains the starteling observation[95] that acetone—reacting slowly with solvated electrons—decreases the radiation chemical yield of solvated, and hence optically detectable electrons, whereas the fast reacting H^+ ions do not[93].

Thus the wide variation of rate constants of the excess electrons in condensed fluid phases is due partly to the electron mobilities covering a range of five orders of magnitude, and partly to the tunnel probabilities which vary from solvent to solvent and from reaction partner to reaction partner and which depend on the overlap of the energy states.

Of course, the kinetics of the electron reactions also can be interpreted in terms of transition state theory, according to which the rate constant of a bimolecular reaction is given by the enthalpy of activation ΔH^* ($\approx E_a$ activation energy) and the entropy of activation ΔS^*

$$k = \frac{RT}{N_L \cdot h} \exp(\Delta S^*/R) \cdot \exp(-\Delta H^*/RT) \tag{21}$$

(R gas constant, h Planck's constant).

Apart from very few exceptions, the activation energy of all electron reactions investigated so far lies in the range of 2 to 5 kcal mol^{-1}[88]; therefore the entropy of activation, *i.e.* the entropy difference between the activated complex and the reactants ($\Delta S^* = S^* - S_{e^-} - S_A$) must be responsible for the variation of the rate constant over so many powers of ten[71, 73]. For high reaction rates, ΔS^* is more positive than for low reaction rates; the general relation between entropy and probability therefore leads back to the concept of tunneling probability which depends on the density of energy states.

According to thermodynamic estimates the entropy of the solvated electrons is more positive by 13 cal mol^{-1} K^{-1} in ammonia than in water[38, 40]. If all other parameters of eq. (21) remain constant, the activation entropy of a reaction in ammonia should be more negative by 13 cal mol^{-1} K^{-1} than in water; in other words the reaction in ammonia should be slower by a factor of 600 than that in water. Differences in the rate constants of this order have been found for some non-diffusion-controlled reactions of electrons with neutral molecules in ammonia and water[96].

The transition state theory describes the pressure dependence of a chemical reaction

$$\frac{d \ln k}{dp} = -\frac{\Delta V^+}{RT} \tag{22}$$

in terms of the activation volume[89] given by the volume difference of the activated complex and the reactants: $\Delta V^+ = V^+ - V_e - V_A$.

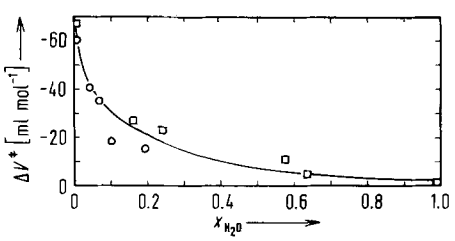


Fig. 18. Activation volume ΔV^+ of the reaction of solvated electrons with water (□ [73]) and with acetonitrile (○ [96]) in water-ammonia mixtures.

In water and alcohols only small effects of pressure on reaction rates are found, *i.e.* the activation volume of the electron reactions is close to zero[44, 45, 97]; in ammonia on the other hand some of the electron reaction rates are increased

up to fifteenfold by application of 1000 bar[73, 96], the activation volume can be up to $-65\,cm^3\ mol^{-1}$; in water-ammonia mixtures values between 0 and -65 are obtained (Fig. 18). The activation volume with inverse sign reflects the cavity volume of the solvated electrons, which is fairly large in ammonia ($R \approx 3\,Å \triangleq V_e \approx 68\ cm^3\ mol^{-1}$), relatively small in water ($R < 1\,Å \triangleq V_e < 3\ cm^3\ mol^{-1}$), and between these values in mixtures of the two, as follows from the absorption spectra (Fig. 13) in connection with theory. Thus the kinetic data support the concept of the cavity model of the solvated electrons (compare Section 2.2).

6.3. Influence of the Dielectric Constant on Ion Reactions

For reactions of electrons with ions, transition state theory leads to a term depending on the dielectric constant ε[89]

$$\ln k = \ln k_\infty + \frac{N_L Z_A e^2}{\varepsilon R T r^*} \tag{23}$$

It describes the electrostatic interaction between charged particles (k, k_∞ rate constant of a reaction in a solvent of dielectric constant ε and in one with $\varepsilon = \infty$, Z_A charge of the ionic reaction partner, r^* radius of the activated complex). Therefore reactions with positive ions ($Z_A > 0$) become slower with increasing dielectric constant because of diminished Coulomb attraction of the oppositely charged particles, whereas those with negative ions ($Z_A < 0$) become faster due to diminished repulsive interaction. The linear plot of $\log k$ *versus* $1/\varepsilon$ in

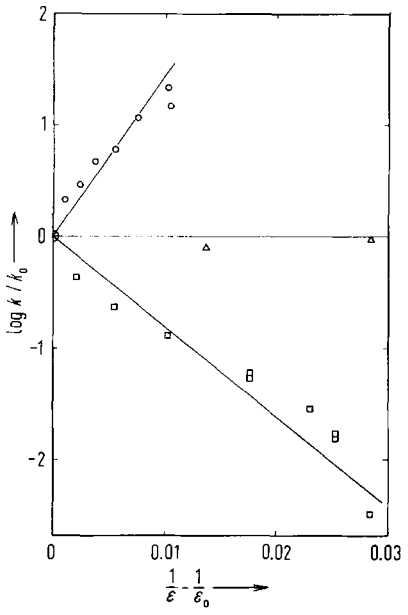


Fig. 19. Inverse dependence of log rate constant k of the reaction of solvated electrons with acetone, nitrate ions, and zinc ions on the dielectric constant ε in water-ethanol mixtures [98] (△ acetone ($Z_A = 0$); □ NO_3^- ($Z_A = -1$); ○ Zn^{2+} ($Z_A = 2$); ε_0 dielectric constant of water, k_0 rate constant of the reactions considered in water).

Figure 19 for several reactions in water-alcohol mixtures[98] ($\varepsilon = 17$ to 80) proves relation (23). The same trend has also been found for reactions in water-ammonia mixtures[96].

6.4. Participation of Solvent in Consecutive Reactions

In some cases the reaction rates have been found to depend on the composition of solvent mixtures, an observation which cannot be interpreted by any of the concepts discussed so far: *e.g.* the reactions of electrons with acetonitrile[96], benzene[99], or fluorobenzene[100] are extremely slow in pure ammonia, but addition of a few mol % of water or methanol leads to a considerable increase in reaction rate: further addition, *e.g.* of water, has a less pronounced effect and finally no effect at all (Fig. 20).

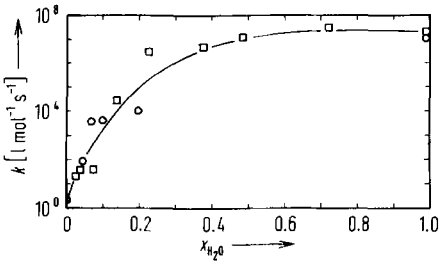


Fig. 20. Rate constant k of the reactions of solvated electrons with benzene (□ [99]) and with acetonitrile (○ [96]) in water-ammonia mixtures.

This solvent dependence of the reaction rate suggests a more complex kinetic situation which might be described by the following reaction mechanism:

$$e^- + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A^- \tag{24}$$

$$A^- + H_2O \xrightarrow{k_3} \text{Products} \tag{25}$$

The electron attachment is formulated as an equilibrium reaction, the resulting radical anion is protonated in a consecutive reaction step by water or alcohol[101] (ammonia with its 10^{14} fold smaller dissociation constant as compared to water can react only slowly, if at all, with the A^- ion). The reaction mechanism [eq. (24) and (25)] leads, with the aid of the concept of the quasi-stationary state, to the experimental rate constant[89]

$$k = \frac{k_1 \cdot k_3\,[H_2O]}{k_2 + k_3\,[H_2O]} \tag{26}$$

which, with appropriate rate constants k_1 to k_3, fits the data of Figure 20. Since electron attachment is an exothermic step, equilibrium (24) is shifted to the right with decreasing temperatures; this would explain the negative activation energy found for some reactions in ammonia rich mixtures with methanol[100].

7. Chemical Equilibria

Chemical equilibria can be observed only in those solvents, which react neither with the excess electrons nor with their reaction products. These are mainly ammonia and its derivatives, and some aliphatic ethers, all of which dissolve alkali metals with formation of excess electrons (viewed thermodynamically, all these systems are unstable; the long lifetime of the excess electrons is due to kinetic hindrance). The electrons

and most of their reaction products have a very short lifetime in reactive solvents; in a few cases the equilibrium constant K ($K=k_1/k_2$) of a reaction like (24) could be obtained by investigation of the rate constants of the reactions in the forward and reverse direction. Owing to the high reducing power of the excess electrons (standard potential *versus* the hydrogen electrode: -1.95 V in ammonia[19, 102, 66b], -2.75 in water[37]), most of the equilibria (24) lie so far to the right hand side that they can hardly be determined.

The equilibrium constant of the reactions of solvated electrons with solvent

$$e^- + NH_3 \rightleftarrows {}^1/_2 H_2 + NH_2^- \quad (27)$$
$$e^- + H_2O \rightleftarrows {}^1/_2 H_2 + OH^- \quad (28)$$

as calculated from the standard potentials at 25°C are of the order of 10^4 and 10^{32} bar$^{1/2}$ l mol^{-1}, respectively; they prove the instability of the dissolved electrons (the equilibrium concentration of electrons in both systems with 1 M base anions and 100 bar hydrogen are about 10^{-5} and 10^{-33} mol^{-1}, respectively). The ammonia equilibrium is shifted to the right by application of pressure[103], whereas the water equilibrium is hardly affected[45]. From the observed data and with

$$\frac{d \ln K}{dp} = -\frac{\Delta V}{RT} \quad (29)$$

it again follows that the electrons create a large cavity in ammonia, but only a small one in water. Both reactions are exothermic ($\Delta H \approx -15$[19] and -50 kcal mol^{-1}[38], respectively), *i.e.* the equilibrium concentrations of electrons increase with increasing temperature.

Quantitative data on equilibria according to (24) are available only for a few aromatic molecules (styrene, naphthalene, phenanthrene, triphenylene) in some hydrocarbons (*n*-hexane, 2,2,4-trimethylpentane, tetramethylsilane). They were obtained by kinetic measurements[91]. The following regularities are observed: electron attachment reactions are connected with negative changes of the free enthalpy, enthalpy, and entropy; *i.e.* the equilibrium constants are larger than 1 ($\Delta G^0 = -RT \ln K$) but decrease with increasing temperature ($d \ln K/dT = \Delta H^0/RT^2$). The standard free reaction enthalpy ΔG^0 ($= G^0_{A^-} - G^0_A - G^0_{e^-}$) is the more negative the higher the electron affinity of the aromatic molecules and the higher the energy of the electrons in the solvents (described by V_0). The entropy decrease indicates that the electrons are less localized in the solvent than in the aromatic molecule (delocalization corresponds to a state of low order or of high entropy) and is therefore also dependent on the size of the molecules.

Not enough data are presently available to yield more information on the thermodynamics of excess electrons and their reactions.

8. Unsolved Problems

The known properties of dissolved electrons can be described qualitatively by theory. Quantitative agreement between experiment and theory, as has been reported now and again, should not be overestimated because the theory is often adapted to fit the experimental results. However, preliminary *ab initio* calculations[104, 105] match some of the experimental results and led to additional information on the structure of the solvent shell of the solvated electrons.

Many problems still remain unsolved. There is no convincing theoretical explanation for the diamagnetic dimer[106], a pair of electrons formed from two paramagnetic solvated electrons by spin compensation. This entity prevails in metal-ammonia solutions of moderate to low concentrations; it has an absorption spectrum differing only slightly from that of the solvated electrons. It might be that the relative stability of this dimer prevents the pseudo-bimolecular reaction of electrons in ammonia; in water this reaction [eq. (15)] decisively restricts the lifetime of the solvated electrons.

Another question concerns the absorption spectra of the electrons which were attributed to the 1s→2p transition: are there further hidden additional transitions to higher levels (3p, 4p...)[106], such as are observed in the hydrogen atom, or is the broad spectrum explained solely by the wide cavity size distribution function as described in Section 5? Moreover, transitions to higher s levels should also be observable, albeit only by two photon absorption[106].

The localized excess electrons detected in helium by mobility studies should also be observable by light absorption[87]. Photoconductivity of the localized electrons which again were observed in helium or some glasses definitely has not been found in liquid ammonia[107], although UV light causes an outer photoelectric effect[108] (transfer of an electron from the solution to the gas phase). Do the nonlocalized electrons in ammonia or water vapor of densities too low for solvation have a higher mobility and modified reactivity compared to their solvated state, as was found for hydrated electrons before full solvation was established[95]?

Since solvated electrons in ammonia can be produced very conveniently by electrochemical means[109] owing to the high hydrogen overvoltage, the electrode kinetics of this reaction and further reduction reactions should be investigated. A quantitative relation might be obtained between reaction rates or equilibria and the energetics of electron reactions. Such investigations cannot be carried out in aqueous systems because hydrogen formation sets in long before formation of dissolved electrons is possible.

The list of unsolved problems relating to excess electrons is long, probably longer than that of solved problems. The efforts to solve outstanding problems is definitely worthwhile, not only in order to answer these academic problems but also because we might touch upon other chemical, biological, or technical aspects, as mentioned in the introduction. Even new industrial processes might result from our endeavors. Two new chemical processes have indeed already been developed on the basis of research relating to dissolved electrons[110]: a process for the safe disposal of poisonous cyanide wastes[111] resulting from tempering baths for steel hardening on a thousand ton per year scale; and a process for the production of heavy water, used as neutron moderator in nuclear power plants with natural uranium fuel[20]. A novel process for the enrichment of the lithium isotope of mass 6 is being developed, which might serve, together with deuterium, for energy production by nuclear fusion (overall reaction $D + {}^6Li \rightarrow 2\,{}^4He + 21$ MeV).

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Pore Sizes of Solids

By István Halász and Kornél Martin[*]

Dedicated to Professor Hermann Hartmann

A new, fast, and simple method based on size exclusion chromatography permits determination of the volumes of open and closed pores of rigid solids such as silica or porous glasses, together with the specific surface and the pore-size distribution for pore diameters ranging from 10 to 4000 Å. The results are in good agreement with those obtained by classical methods (capillary condensation, mercury porosimetry).

1. Introduction

The determination of the pore-size distribution of catalysts, absorbents, and other solids of technological significance is an important task which, however, is frequently very time-consuming. The fundamentals of the classical methods such as capillary condensation and mercury porosimetry will first be briefly outlined.

Given a knowledge of the sorption isotherm of nitrogen on solids at the temperature of its atmospheric boiling point[1], it is then possible to assign a pore diameter ϕ[***] to the adsorbed mass (volume) which corresponds to the relative pressure p/p_0, assuming that capillary condensation takes place. Neglecting the layer adsorbed prior to the commencement of the capillary condensation, it is possible to calculate ϕ according to

$$\phi\,[\text{Å}] = \frac{8.28}{\log p_0/p} \tag{1}$$

where p_0 is the vapor pressure and p the equilibrium pressure of nitrogen[2]. If the adsorbed layer is also taken into consideration, the ϕ-value calculated from eq. (1) increases as a function of the pressure, *e.g.* by an increment of 9 Å at $p/p_0 = 0.2$ and by an increment of 40 Å at $p/p_0 = 0.9$[2]. However, the accuracy of the measurements decreases with increasing relative pressure, so that in practice it is only possible to use this method for a pore diameter range of 20 to 200 Å (and at the most up to 400 Å).

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[***] Here and in the following it is arbitrarily assumed that the pores are cylindrical.

Comparison of the adsorption isotherms for a nonporous solid and a microporous material ($\phi < 20$ Å)—the "t-method"—allows an approximate determination of the pore-size distribution in the microporous substances[3].

In mercury porosimetry the penetration of mercury into the solid under pressure is measured[4, 5]. By using the empirical approximation:

$$\phi\,[\text{Å}] = \frac{150000}{p\,[\text{atm}]} \tag{2}$$

it is possible to calculate the pore diameter ϕ as a function of the applied pressure p. Because of instrumental difficulties, so far it has only been possible to determine pore diameters greater than 75 Å. Since the measurements require pressures of up to 2000 atm, the results are falsified if the material collapses during the determination.

In order to establish the complete pore-size distribution, the results of capillary condensation and mercury porosimetry should partly overlap for each specimen. The apparatus required is expensive, as is its maintenance, and in addition the measurements on just a single sample may take as long as 30 h. With these classical methods a precise determination of the pore-size distribution of fine-grain solids (mean particle size $d_p < 20\,\mu$m) is often difficult.

The specific surface and the mean pore diameter (but not the pore-size distribution) of porous materials may also be determined by small-angle X-ray scattering[6, 7].

Below we shall describe a new method for the determination of the pore-size distribution in solids by size exclusion chromatography (SEC)[8, 9], which requires simpler equipment and is less time-consuming than the classical methods. Further advantages of the SEC method are that the measurements are not carried out at very low temperatures (−183 °C) or

very high pressures (2000 atm or more) and that the mass transport phenomena are similar to those that occur in adsorption and catalytic processes.

Finally, it should be noted that it is also possible to use the SEC method for the examination of solids that have been swelled in solvents, *i.e.* for materials that could be examined by classical methods only in the dry state. Examples of such materials are the copolymers of styrene and divinylbenzene.

At this stage it is appropriate to draw attention to the different boundary conditions that must be assumed to exist both in the classical methods and in the new method.

2. Size Exclusion Chromatography

Size exclusion chromatography (SEC)[10], frequently also referred to as gel-permeation chromatography[11], gel-filtration chromatography[12], or molecular sieve chromatography[13], makes it possible to separate mixtures dissolved in the mobile phase according to molecular size. To this end the eluent must be such that the molecules of the substance under test are not sorbed by the solid stationary phase. The method is generally used for the separation of polymer mixtures, though this is not an invariable rule.

Swellable polymers (gels) were originally used as the stationary phases. Later on solids with a rigid matrix (*e.g.* porous glasses or silica gels) were also employed, whose pore structure could be determined by means of classical methods[14]. The quality of these stationary phases was often characterized by SEC itself. For this purpose the logarithm of the weight-average molecular weight $\bar{M}_w$ of the polymer substances was usually plotted as a function of the elution volume V_e[15–25]. The polymers were then assigned "rotation coil diameters" as a function of $\bar{M}_w$[15–17, 19, 21, 25]. Such calculated and variously defined "radii" of "monodisperse" polymeric test materials were likewise called upon for the characterization of column packings as a function of the elution volume V_e[16, 17, 19, 21, 24]. In the case of stationary phases with a rigid matrix the results were comparable with the pore-size distributions determined by the classical methods[15, 18, 19, 25].

In classical exclusion chromatography the pore structure of the stationary (solid) phase is thus known; what is to be determined is the molecular-weight distribution of the polymer mixture dissolved in the eluent.

Surprisingly, the inverse procedure—*i.e.* the determination of the pore-size distribution of a rigid solid by means of exclusion chromatography—has not yet been reported. In this method the molecular weights of the "monodisperse" polymers are known.

3. Boundary Conditions of the Method

In what follows we assume that for a given column geometry and pore structure of the packing the elution volume V_e of a test material is a function only of the molecular size of this test material. However, this can only be a justifiable assumption if the following essential boundary conditions are fulfilled:

1) The test material is not adsorbed on the solid surface.
2) There is a reversible "quasi"-distribution equilibrium[26] of the test material between the flowing eluent and the eluent held within the pores of the solid packing. This equilibrium is established instantaneously, provided that the linear flow velocity of the eluent is sufficiently small and that the column is not overloaded with the test material.
3) The probability that the test material is present in the flowing eluent or in the stagnant eluent inside the pores is proportional to the volume of the flowing eluent (interstitial volume) and to the pore volume accessible to the test material. This is equivalent to saying that the Bunsen distribution coefficient between the two phases is unity.
4) The elution peak approximates closely to a Gaussian curve.
5) The matrix of the solid is rigid. It neither swells nor shrinks, and the solid's pore-size distribution is not affected by changes in the eluent or in the eluent pressure.

In addition, there is a necessary boundary condition that the working temperature and the flow velocity of the eluent are kept constant, and that sample injection is instantaneous.

The condition that no adsorption of the test material occurs from a number of eluents could be demonstrated experimentally for polystyrene standard and silica gels from various sources. Within the limits of experimental error, the elution volumes of benzene or polystyrene samples were independent:

a) of the flow velocity of the eluent (1—5 mm/s, for particle sizes of the solid smaller than 100 μm);
b) of the sample concentration at the column inlet (*i.e.* independent of the sample volume), provided that the column was not overloaded and that the sample concentration in the eluent was less than about 300 ppm;
c) of the eluent polarity (dichloromethane, chloroform, tetrahydrofuran, dimethylformamide), even though the dielectric constants of these eluents differ widely;
d) and of whether the samples were started and run individually or as a mixture. This made it possible to largely exclude the mutual interactions of the polymer molecules.

Other authors[27] had already pointed out that no measurable molecular-weight-dependent adsorption of polystyrene samples (standard) occurred on polystyrene gels with chloroform (at 35°C) or *o*-dichlorobenzene (at 87°C) as the eluent.

4. Experimental Conditions

The basic principles, apparatus, and measurement method of exclusion chromatography[13, 28] are almost identical with those in high-pressure liquid chromatography[29, 30]. In the work described here, for example, the following components were set up in series: a high-pressure pump with a constant flow rate (M 6000, Waters Associates, Inc., Milford, Ma., USA), a sample injector (U6K, Waters Associates, Inc.) for sample volumes between 0.5 μl and 2 ml, a stainless steel tube (separation column)[31] with a drilled-out internal diameter of 4.2 mm, and a UV detector of our own design (254 nm, cell volume 10 μl)[31] (see also [32]). All the measurements were carried out at room temperature.

The flow rate through the pump was constant to $\pm 1\,\%$ during the longest elution times. By measuring the breakthrough (elution) times t_e of the individual samples it was possible to determine the elution volumes V_e with an accuracy of $\pm 1\,\%$ or better.

The column is packed with the solid whose pore-size distribution is to be determined. In order to achieve a sufficiently homogeneous packing density along the column, experience has shown that the column should be packed wet[31,33–35] for a mean particle size $d_p < 20\,\mu m$ and dry[36,37] for particles with $d_p > 20\,\mu m$[36,37]. The sieve fractions of the solid may be relatively broad: the lower limit may be 40 % below and the upper limit 40 % above the arithmetic mean of the sieve fraction. Thus, a sieve fraction of 30 to 70 µm is acceptable. The column length required (30 to 100 cm) decreases with decreasing particle size. The column must be designed in such a way that it corresponds to at least 200 (and preferably 500) theoretical plates n[13]. Experience has shown that it is best to pack the columns with sieve fractions whose arithmetic mean lies between 25 and 80 µm. If the particles are smaller they should be packed wet, if they are larger then the column should be made longer than 1 m (because the increased particle size reduces the number of theoretical plates) and the linear velocity of the eluent be reduced (because of the longer diffusion distances). The elution times are thus extended.

The standard test materials were benzene and polystyrenes with various degrees of polymerization in dichloromethane (1—10 mg/ml). The polydispersity ($\bar{M}_w/\bar{M}_n$)[38] of the polystyrenes (Waters Associates, Inc.), where $\bar{M}_w$ and $\bar{M}_n$ are the weight-average and number-average molecular weights, had an average value of around 1.1[27].

The standards were applied to the separation column packed with the solid either singly or in combination (*ca.* 1 µl of solution per component) and the elution volumes were determined. The elution volume is defined by the peak maximum. This requires that the peak be symmetrical; an asymmetry factor As[2][31] smaller than 2 is required. Peak asymmetry may be caused by

- a poor column packing,
- an insufficient number of theoretical plates,
- excessive sample volume (overloading of the column),
- adsorption of polystyrene on the solid packing, and
- an impermissibly high polydispersity of the polystyrene.

The calibration series was made up using polystyrenes of known molecular weight, since these polymers are commercially available from several sources within a wide range of $\bar{M}_w$ (600—3 700 000) and with low polydispersity.

Dichloromethane or chloroform (in exceptional cases tetrahydrofuran or dimethylformamide) were used as the mobile phase (eluent). The relative humidity of the eluents must be below 60 %, as erroneous values may otherwise be obtained because a proportion of the pores is filled with water[39]. When dimethylformamide is used as the eluent a differential refractometer (Waters Associates, Inc., cell volume 10 µl) should be used in place of the UV detector. In series measurements the linear velocity of the benzene sample is between 0.1 and 0.5 cm/s (0.7—3.5 cm^3/min). The pressure drop required to attain this velocity is less than 100 atm. As the flow velocity increases, the number of theoretical plates becomes smaller and the bands may become asymmetric. For a given sieve fraction and column length, the eluent flow velocity used is the highest at which the bands of all the test substances still remain sufficiently symmetrical.

5. Principles of the Method[*]

A portion of the eluent in the separation column fills the voids between the particles of the packing (the interstitial volume V_z) and passes through the column in the axial direction.

The volume fraction V_p is the pore volume, *i.e.* the volume of eluent that has penetrated the pores of the solid. A ϕ-value was assigned to all the polystyrenes of the calibration series (standard) and benzene. This magnitude ϕ [Å] defines the smallest pore diameter into which a standard sample of molecular weight M_i can diffuse "unhindered". The distribution equilibrium between the flowing eluent and the eluent present in the pores is then set up instantaneously.

Naturally, none of the molecules of the standard material of molecular weight M_i can penetrate pores with diameters smaller than ϕ_i. This means that the ϕ-values should be regarded as "exclusion values".

If the molecules of the standard are too large to enter the pores, they pass axially through the column with the linear velocity of the moving eluent. The elution volume of such a standard will be the smallest of all possible elution volumes ($V_{e,min}$). Since in the method described here we work with a homologous series of standard materials, an increase in the molecular weight $\bar{M}$ results in an increased ϕ-value

[*] The most commonly used symbols are listed below:

d_p	mean particle diameter of a disperse solid
ε_c	volume fraction of closed pores in a separation column
ε_p	pore-porosity; fraction of the pore volume in a separation column
ε_s	fraction of the solid skeleton volume in a separation column
ε_T	total porosity; volume fraction of the separation column occupied by the eluent
ε_z	interstitial porosity; fraction of the interstitial volume in a separation column
F	flow rate of the eluent
m	mass of the solid packing in a separation column
$\bar{M}_n$	number-averaged molecular weight
$\bar{M}_w$	weight-averaged molecular weight
n	number of theoretical plates in a separation column
O_{sp}	specific surface
ϕ	pore diameter (assuming the pores to be cylindrical); also the exclusion value of a polymer standard
$\bar{\phi}$	geometric mean of the exclusion values of two consecutive standards in the calibration series
ϕ_m	mean pore diameter (calculated assuming a log-normal distribution)
ϕ_r	calculated coil diameter of a polymer standard
ψ	void fraction; volume ratio of open pores to the nominal solid volume (solid + pores)
R	sum of residues; fraction of the total pore volume accessible to a molecule with an exclusion value of ϕ.
ρ_s	true density of the solid
t_e	elution time, breakthrough time of a polymer standard
u	cross-section-averaged linear velocity of the eluent
V_c	volume of pores inaccessible to the eluent
V_e	chromatographic elution volume of a polymer standard
$V_{e,max}$	maximum elution volume in a calibration series (elution volume of the standard with the lowest molecular weight)
$V_{e,min}$	minimum elution volume in a calibration series (elution volume of the standard with the highest molecular weight)
V_k	volume of the empty separation column
V_p	pore volume; volume of eluent that has penetrated the pores
$V_{p,s}$	specific pore volume; = pore volume per gram of the solid
V_s	skeletal volume of the solid (without the pore volume)
V_z	interstitial volume; volume of eluent flowing in the axial direction

of the polymer. In accordance with this nomenclature we obtain $V_{e,min}$ with $\bar{M}_{max}$ and ϕ_{max}. The largest elution volume $V_{e,max}$ corresponds to the standard sample with the lowest molecular weight ($\bar{M}_{min}$) and the smallest exclusion value (ϕ_{min}).

The volume of the empty separation column V_k is the sum of the volume of the solid skeleton V_s, the volume V_c which represents the pores inaccessible (closed) to the eluent, the interstitial volume V_z, and the pore volume V_p (see above):

$$V_k = V_z + V_p + V_s + V_c \tag{3}$$

The volume V_k is readily determined from the column geometry. It follows from the above definitions that V_z must be determined by:

$$V_z = V_{e,min} \tag{4}$$

According to eq. (4), the volume of pores with a diameter greater than ϕ_{max} is contained in the interstitial volume V_z. The V_z values determined by size exclusion chromatography may therefore be larger than those obtained by mercury porosimetry.

The rule for the determination of the total pore volume V_p likewise follows from the definitions given above:

$$V_p = V_{e,max} - V_{e,min} \tag{5}$$

By using standards of arbitrary $\bar{M}$ and ϕ-values between the two limits it becomes possible to determine the pore-size distribution of rigid solids. For example, determination of the evolution volumes of two standard samples with molecular weights $\bar{M}_1$ and $\bar{M}_2$ (where $\bar{M}_1 < \bar{M}_2$) gives the relationship $\Delta V = V_{e,1} - V_{e,2}$. ΔV is the volume of the pores within the column that have a diameter greater than ϕ_1 and smaller than ϕ_2.

The total pore volume of the solid, V_p, is determined by at least three parallel measurements in which standards with $\bar{M}_{min}$ ($V_{e,max}$) and $\bar{M}_{max}$ ($V_{e,min}$) are initially injected into the column together. The elution time t_e and the flow velocity F are measured at the same time. The reproducibility of the elution volume for benzene ($V_{e,max} = F \cdot t_{e,max}$) must be better than $\pm 1\,\%$. The subsequent measurements with the remaining standards are referred to $V_{e,max}$, which enables one to do without the rather cumbersome measurement of the flow velocity in subsequent determinations. Benzene is injected simultaneously with each polystyrene standard mixture and its elution time $t_{e,max}$ is used for normalization. How many standards may be injected simultaneously depends on the sharpness of the separation (number of theoretical plates n). The elution volumes of the standards are generally determined by taking the mean value from several chromatograms. The accuracy of the elution volumes—especially that of their differences—measured in this way is better than $\pm 0.5\,\%$.

The skeletal volume V_s is calculated from the mass m of the solid material in the column and from its true density ρ_s. The true density of a solid may be determined, for example, volumetrically with helium or by X-ray diffraction[40].

Finally, V_c (the volume of the closed pores) may be calculated from eq. (3). The value of V_c is subject to relatively large error due to small differences between large numbers. Experience has shown that the calculation of V_c is meaningful only when V_c/V_k is greater than 0.05.

The results become rather more general if use is made of the ratio of volumes (the porosity ε) in place of the volumes themselves:

$$\varepsilon_i = V_i/V_k \tag{6}$$

For example, the interstitial porosity $\varepsilon_z = V_z/V_k$ is the fraction of the free column cross-section area available to the eluent flowing in the axial direction. The pore porosity $\varepsilon_p - V_p/V_k$ is the pore volume relative to the volume of the empty column. The total porosity

$$\varepsilon_T = \varepsilon_z + \varepsilon_p \tag{7}$$

is the fraction of the free column cross-sectional area occupied by the flowing eluent and the eluent present within the pores.

In order to make the values independent of the column packing dimensions, we introduce the void fraction ψ[21]:

$$\psi = \frac{\varepsilon_p}{1-\varepsilon_z} \tag{8}$$

The void fraction expresses the proportion of the total solid volume contributed by the pores. The mass m of the solid in the column may be calculated from:

$$m = (1-\varepsilon_T-\varepsilon_c)\rho_s V_k \tag{9}$$

Neglecting the volume of the closed pores ($\varepsilon_c = 0$),

$$m \approx (1-\varepsilon_T)\rho_s V_k \tag{9a}$$

However, eqs. (9) and (9a) should be used with considerable caution, because $(1-\varepsilon_T-\varepsilon_c)$ and $(1-\varepsilon_T)$ are small differences between large numbers. The mass of solid m may be determined with much greater accuracy if the column packing is carefully removed at the end of the measurements, dried, and weighed. From the value of m, we can obtain ε_c by means of eq. (9). The greatest source of error lies in the fact that the true density ρ_s of the solid is very seldom accurately known. The true density of silica gel is around $2.3\,g/cm^3$. If an error of $\pm 10\,\%$ in ρ_s is accepted, the error in the determination of the closed-pore volume (V_c) is smaller than $\pm 2\,\%$, since the skeletal volume V_s as determined using ρ_s ($V_s = m/\rho_s$) is generally less than 20 % of the column volume V_k. In some silica gels V_c was up to 9 % of the column volume V_k and up to 30 % of the total pore volume V_p.

6. The Calibration Curve

The elution volumes V_e of the polystyrene standards of the calibration series were determined on several silica gels

whose relatively narrow pore-size distributions had been determined in other laboratories by the classical methods[*].

Exclusion values (pore diameters ϕ) were now assigned by trial and error to the standards of the calibration series, in such a way that the maxima of the pore-size distribution curves as measured by exclusion chromatography agreed with the values obtained by "classical" measurements.

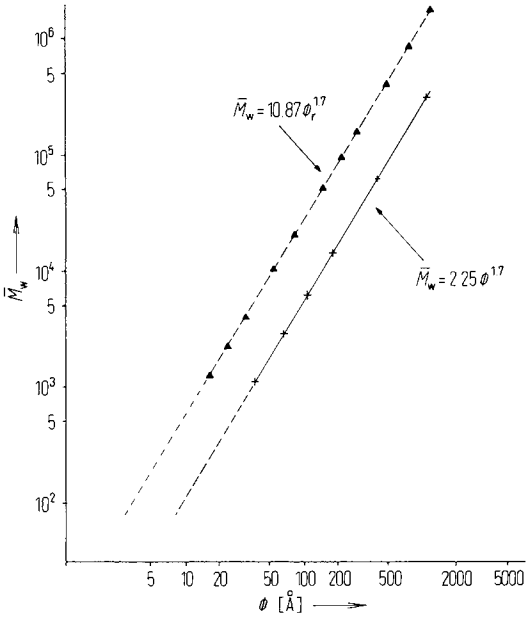


Fig. 1. Calibration curve (——) for the assignment of molecular weights $\bar{M}_w$ of the standards to exclusion values (=pore diameters) ϕ of silica gels. The calibration curve was obtained by comparing the maxima of the pore-size distribution measured by SEC (standards: polystyrenes and benzene; eluent: CH_2Cl_2; solid: various silicas and porous glasses) and the maxima determined by "classical" methods. (– – – –) Correlation of the $\bar{M}_w$ of polystyrene and the coil diameter ϕ_r in THF (after measurements by *Kreveld* and *van den Hoed* [21]).

If $\log\bar{M}_w$ is plotted against the $\log\phi$ values thus obtained (Figure 1; continuous line), then the points are found to lie on a straight line closely described by the equation

$$\bar{M}_w = 2.25\,\phi^{1.7} \tag{10}$$

where ϕ is expressed in Å. Eq. (10) gives ϕ to good approximation as:

$$\phi\,[\text{Å}] \simeq 0.62(\bar{M}_w)^{0.59} \tag{11}$$

According to eq. (11), benzene was arbitrarily assigned an exclusion value of $\phi = 8.1$ Å. Strictly speaking, the numerical values given in eqs. (10) and (11) are valid only for dichloromethane, but they should also be good approximations for other "good" solvents. The first two columns of Table 1 give the molecular weights $\bar{M}_w$ for polystyrene of the calibration series and the ϕ-values assigned by means of the calibration line.

Table 1. Pore diameters (=exclusion values) ϕ assigned to the benzene and polystyrene standards, elution volumes V_e, and the sum of residues R. Solid: Merckogel SI 100; sieve fraction 7–11 µm; $V_k = 4.717\,cm^3$; $\varepsilon_p = 0.382$; $\varepsilon_c = 0.047$; $\psi = 66.4\,\%$; $\varepsilon_z = 0.423$; $\varepsilon_T = 0.805$; $\varepsilon_s = 0.147$; $m = 1.59$ g.

$\bar{M}_w$	ϕ [Å]	V_e [µl]	R [%]	ΔV_e [µl]	ΔR [%]	$\bar{\phi}$ [Å]
Benzene	8	3802	100.0			
				269	14.9	15
600	26.7	3533	85.1			
				287	15.9	39
2100	55.9	3246	69.2			
				156	8.6	68
4000	81.6	3090	60.6			
				406	22.5	107
10000	140	2684	38.1			
				282	15.6	173
20800	215	2402	22.5			
				175	9.7	253
36000	297	2227	12.8			
				86	4.8	414
111000	576	2141	8.0			
				38	2.1	685
200000	815	2103	5.9			
				25	1.4	1070
498000	1400	2078	4.5			
				18	1.0	1640
867000	1930	2060	3.5			
				54	3.0	2670
2610000	3700	2006	0.5			
				9	0.5	4090
3700000	4530	1997	0			

Polystyrenes are linear polymers which in solution may be regarded as random coils. On the basis of polymer-statistical considerations[41] and the results of light-scattering measurements[42], *Kreveld* and *van den Hoed*[21] tabulated the calculated coil diameters ϕ_r for polystyrenes in tetrahydrofuran (THF). Fig. 1 shows a log-log plot of $\bar{M}_w$ *vs* ϕ_r. The broken straight line may be described by the equation:

$$\bar{M}_w = 10.87(\phi_r)^{1.7} \tag{12}$$

Since THF is considered a "good" solvent, just like dichloromethane, one would expect similar ϕ-values for the latter.

It may be seen from Eqs. (10) and (12) that the pore diameter ϕ of a solid assigned by us to a standard polystyrene of molecular weight $\bar{M}_w$ is 2.5 times as large as the coil diameter ϕ_r of molecules of the same polystyrene[21]. To put it in another way, the rotational coil diameters ϕ_r must be some 2.5 times smaller than the diameter of the pores in the solid to allow the polymer unhindered access to the pores (*i.e.* to enable "instantaneous equilibrium" to be achieved). The actual numerical value of this factor is open to discussion. *Cantow* and *Johnson*[15] had pointed out earlier that the factor should be 2 or more. The work of *Verhoff* and *Sylvester*[43] suggests a factor of 2.5[44]. Measurements on a porous glass have yielded a factor of 2 to 2.5[45,46]. On the other hand, *Yau et al.* state in the same publication[46] that "the shape of the GPC calibration curve for flexible polymer molecules is different from the pore size distribution curve of the packing".

[*] "Merckogels" (E. Merck AG, Darmstadt) with most frequent pore diameters (pore volume maxima) of around 60, 100, 200, 500, and 1000 Å and sieve fractions of around 10 µm; CPG-10 (Controlled Pore Glass, Serva, Heidelberg) with most frequent pore diameters of around 75, 170, 500, 1000, and 2000 Å and sieve fractions of 37—74 µm; silica gels prepared by Prof. *K. Unger* (Eduard-Zintl-Institut, Technische Hochschule Darmstadt) and in our own laboratory, with sieve fractions of around 10 µm. In the CPG-10 series only the most frequently occurring pore diameters were known, while the complete pore-size distribution curves had been available for the other products.

7. Determination of the Specific Surface of Silica Gels

Assuming that the pores are cylindrical and continuous (*i.e.* open at both ends), the specific surface O_{sp} is given by:

$$O_{sp}[cm^2/g] = \frac{4\,V_{p,s}[cm^3/g]}{\phi_m[cm]} \tag{13}$$

where $V_{p,s}$ is the specific pore volume and ϕ_m the mean pore diameter calculated from the Gaussian distribution. If the pores are not all open, the error in the specific surface is less than 5 %, provided that the cylindrical pores are 5 times as long as their diameters.

For the sake of convenience eq. (13) is written in the form:

$$O_{sp}[m^2/g] = \frac{40\,V_{p,s}[\mu l/g]}{\phi_m[\text{Å}]} \tag{13a}$$

If the results of measurements by SEC are compared with the BET surfaces[1], it is our experience that the discrepancy is less than 5 %, at least for silica gels with $O_{sp} > 300\,m^3/g$. For silica gels with smaller specific surfaces the available measurements are still insufficient.

8. Experimental Results

Figure 2 illustrates the determination of elution volumes on a particularly favorable example. The pore volume of the silica gel used here was unusually high ($2.07\,cm^3/g$) and the particle diameter was small (10–15 μm). About 3000 theoretical plates were obtained for benzene in a separation column 30 cm in length. It was thus possible, in this case, to determine the elution volumes of seven components in a single measurement. In routine determinations benzene and one or two of the 12 polystyrene standards are injected simultaneously. The determination of the 13 elution volumes in duplicate takes about an hour under routine conditions.

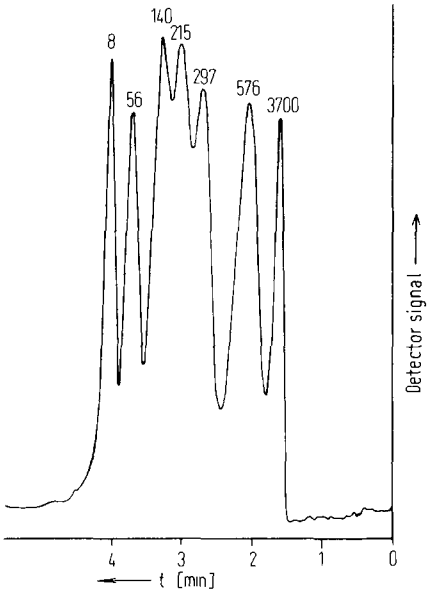


Fig. 2. Elution volumes V_e of some polystyrene standards on silica gel. The peaks are characterized by the assigned values of pore diameter ϕ [Å]. Solid: silica gel (Prof. *Unger*, Darmstadt, 733 Hk 4b): specific surface O_{sp}: $285\,m^2/g$; pore volume: V_{sp}: $2.07\,cm^3/g$; $\varepsilon_z = 0.37$; $\varepsilon_p = 0.55$; sieve fraction: 10–15 μm; packing density: $0.266\,g/cm^3$. Column: internal diameter 4.34 mm, length 30 cm, volume of empty column $V_k = 4.43\,cm^2$.—Eluent: dichloromethane. $\Delta p = 22$ atm; $u = 1.25$ mm/s.—Amount of sample per component: 0.5–1 μg (0.5–1 μl of solution in CH_2Cl_2); UV detector (254 nm): full scale deflection $= 4 \times 10^{-2}$ extinction units; number of theoretical plates for benzene: 3000.

The record of a typical run is reproduced in the first three columns of Table 1. Based upon the standards available, only the pores with an entrance diameter of more than 8 Å and less than 4530 Å are included in the total pore volume. Table 1 enables us to calculate a pore volume $V_p = (3802 - 1997) = 1805\,\mu l = 1.805\,cm^3$, and a porosity $\varepsilon_p = 1805/4717 = 0.38$. Similarly, the ε_z of the sample with the highest molecular weight ($\phi = 4530$ Å) was found to be $1997/4717 = 0.42$ from the elution volume. ε_c was calculated with the aid of eq. (9). It follows from eqs. (3) and (6) that:

$$\varepsilon_z + \varepsilon_p + \varepsilon_c + \varepsilon_s = 1 \tag{14}$$

ε_s was calculated by means of this equation and the void fraction ψ was obtained from eq. (8). The specific pore volume follows from $V_{p,s} = V_k \varepsilon_p / m$. In order to facilitate checking, Table 1 gives the calculated values with an accuracy greater than the limits of error of the SEC method permit.

9. Possible Methods of Presentation of the Pore-Size Distribution

Experience has shown that the pore-size distribution of many solids may best be illustrated by a log-normal distribution curve. Figure 3 shows a plot of the sum of residues R (column 4 in Table 1) as a function of $\log\phi$ (calculated according to column 2).

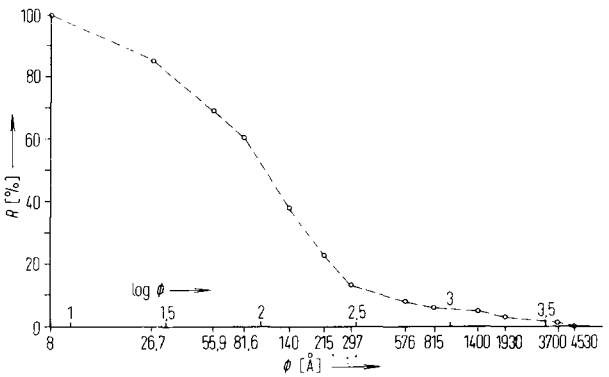


Fig. 3. Sum of residues distribution of the pore diameters of Merckogel SI 100 silica gel (integral distribution curve). For the parameters see Table 1 (see text).

The sum of residues R of a given pore diameter ϕ_i is defined as the fraction of total pore volume V_p formed by all the pores with a diameter greater than ϕ_i. A sum of residues of 38.1 % at a pore diameter of 140 Å, for example, means that the volume of pores whose diameter exceeds 140 Å constitutes 38.1 % of the total pore volume. Figure 3 may also be regarded as an integral distribution curve.

From the values of ΔR (column 6 of Table 1) we may, for example, read off that 15.6 % of the total pore volume should be assigned to pores whose diameter ϕ is between 140 and 215 Å. Because of the log-normal distribution this

pore volume is by definition assigned to the geometric mean value of 140 and 215 Å ($\phi = 173$ Å). The ϕ-values corresponding to ΔV_e are found in the last column of Table 1. The absolute frequency may be represented by a plot of ΔV_e against $\log\bar{\phi}$.

In the present calibration series with polystyrene standards the distances between $\log\bar{\phi}$ and the ratio of the ϕ-values are comparatively large and not equal. For this reason we present the relative frequency by plotting

$$100 \times \frac{\Delta V_e}{V_p} / \Delta \log\phi$$

against $\log\phi$; such a "difference distribution curve" has greater information value[47]. Figure 4 (broken line) shows the relative frequency of the pore diameters for a silica gel.

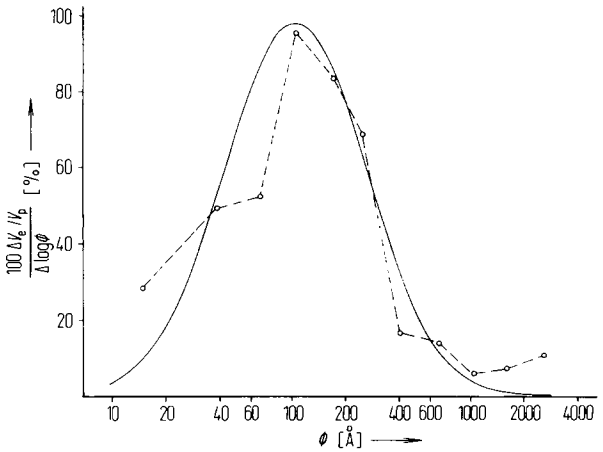


Fig. 4. Relative frequency (---) of the pore diameters of Merckogel SI 100 silica gel (difference distribution curve). (——) Gaussian curve obtained by evaluation of Fig. 5. For the parameters see Table 1.

By introducing the sum of residues R as a function of $\log\phi$ (plot on probability graph paper) one obtains a straight line by means of which it is possible to calculate the mean pore diameter ($\log\phi_m$) and its standard deviation ($\log\sigma$). Such presentation (Figure 5) enables us to determine $\log\phi_m = 2.02$

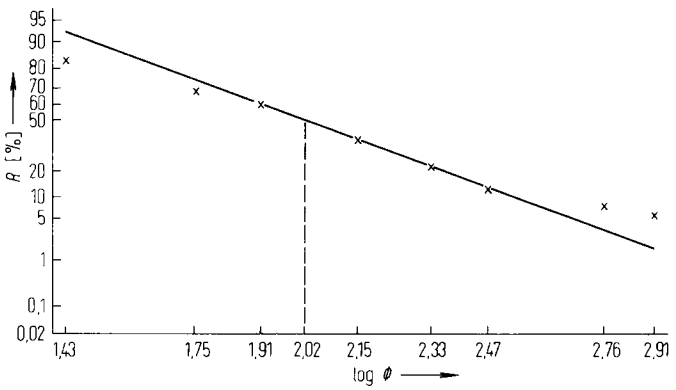


Fig. 5. R and $\log\phi$ (measured values taken from Table 1) for Merckogel SI 100 silica gel, plotted on probability paper.

and $\log\sigma = 0.40$ for Merckogel silica gel (SI 100). The mean pore diameter ϕ_m is thus 105 Å. The Gaussian curve calculated on the basis of these values is likewise shown in Figure 4 (continuous line). The small scatter of the values around the straight line in the probability plot (Figure 5) indicates that the assumption of a log-normal distribution is an acceptable approximation. The calculation of the mean pore diameter from the differential distribution curve gave a value of 107 Å. Such good agreement of the ϕ_m-values must be regarded as fortuitous.

Experience has shown that the deviations may amount to 30%. This will be illustrated by means of an example. Figure 6 shows the relative frequency and the Gaussian curve

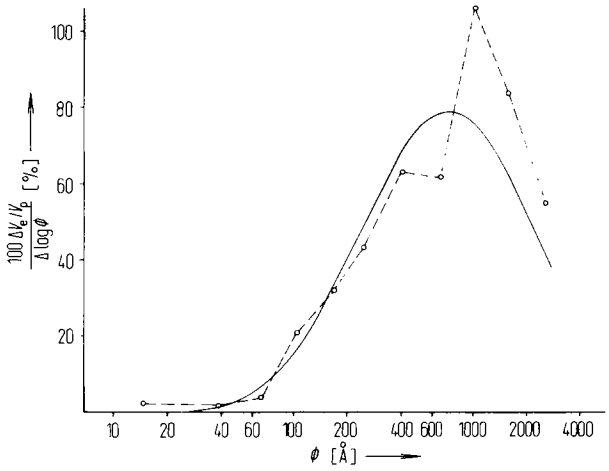


Fig. 6. Relative frequency (---) of the pore diameters of Merckogel SI 100 silica gel. Pore volume V_{sp}: 0.80 cm³/g, $\varepsilon_z = 0.443$; $\varepsilon_p = 0.365$; sieve fraction: 10 µm; packing density: 0.46 g/cm³. Experimental conditions as in Fig. 2. (——) Gaussian curve.

for the pore diameters of a silica gel with large pore diameters. Values of 1070 and 741 Å were obtained here for the mean pore diameter ϕ_m, indicating that in this case the log-normal distribution is only a very rough approximation. It is not impossible that the pore structure had been formed here by two different processes. When comparing the two areas between the limits of 14.7 and 2670 Å, we should note that the difference curve (broken line) within these limits has been normalized to 100, while the Gaussian curve is normalized to 100 between $-\infty$ and $+\infty$.

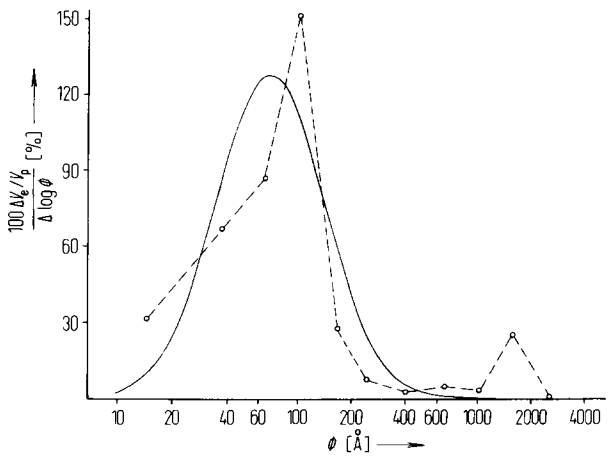


Fig. 7. Relative frequency (---) of the pore diameters of Controlled Pore Glass CPG-10-75 Å; pore volume V_{sp}: 0.50 cm³/g; $\varepsilon_z = 0.444$; $\varepsilon_p = 0.313$; sieve fraction: 37—74 µm; packing density: 0.62 g/cm³. Column length 30 cm. Number of theoretical plates for benzene: 220 at $u = 3.2$ cm/s. (——) Gaussian curve.

In order to illustrate the wide applicability of the method, Figure 7 shows the pore-size distribution of a porous glass. The specific pore volume is here small (0.50 cm^3/g) and the material was available only in the form of a relatively coarse fraction (37—74 μ). The mean pore diameter taken from the Gaussian curve ($\phi_m = 72$ Å) is in good agreement with the value of 84 Å given by the manufacturer. This example also points to some limitations of the method. At a linear eluent velocity of 32 mm/s the 30 cm long separation column has no more than 220 theoretical plates for benzene. Despite the relatively broad elution bands, it was possible to determine the elution volumes V_e in an entirely acceptable manner.

10. Concluding Remarks

The exclusion chromatography method described here allows a quick and simple determination of many morphological properties of solids. The measurements may be carried out under the usual conditions of application of the solids, *e.g.* in catalysis or chromatography. Extremely high pressures and low temperatures are unnecessary. In contrast to the classical methods, the SEC method enables us to determine the pore-size distribution within the entire range of (so far) 10 to 4000 Å.

There is excellent experimental agreement with the results for the specific pore volumes and the mean pore diameter ϕ_m obtained by classical methods, while the agreement with respect to the specific surface is adequate.

Experience has also shown that, for a given solid, capillary condensation, the mercury porosimetry, and the SEC method yield increasingly broad pore-size distributions. This seems to be due to the different boundary conditions of these methods and will not be discussed here.

The SEC method is applicable only if the solid to be investigated can be packed into a separation column and if sorption of the polymer standards can be excluded.

The SEC method has so far been applied to silica gels, porous glasses, aluminum oxides, and tungsten oxides[8]. Preliminary experiments suggest that the method may also be used for the determination of the pore-size distribution in swollen solids such as polystyrene gels. In such cases the pore structure may be a function of the swelling liquid. No such measurements are possible by the classical methods.

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Superacid-Catalyzed Oxygenation of Alkanes[1]

By Georg A. Olah, David G. Parker, and Norihiko Yoneda[*]

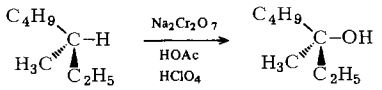
New synthetic methods (26)

Owing to the ready availability of the starting materials, the functionalization of saturated hydrocarbons for preparing chemical intermediates and products represents an attractive goal. The possibility of converting alkane in a controlled way into alcohols, ketones *etc.*, *i.e.* to oxyfunctionalize them, is particularly challenging. After a short account of previous methods used for the oxidation of alkanes, particular emphasis will be given to recently developed reactions of alkanes with oxygenating agents in superacidic media.

1. Older Methods of Oxidation

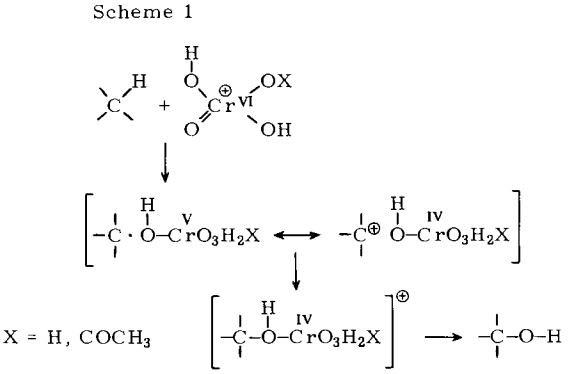
1.1. Chromic Acid Oxidations

Chromic acid has found wide applicability as an oxidizing agent in organic chemistry[2]. Its reactions with alkanes has been extensively studied, and its selectivity in attacking tertiary C—H bonds forms the basis of the Kuhn-Roth determination of the number of *C*-methyl groups in a molecule[3]. Essentially this procedure consists of oxidizing the substrate molecule with hot chromic acid, and from the resultant mixture acetic acid and higher homologues are recovered. The yields of these acids give a measure of the number of *C*-methyl groups present. The original method has undergone a number of modifications[4], for example addition of vanadium pentoxide or manganese(II) sulfate in the oxidation[5]. Although it has largely been superceded by instrumental methods such as NMR spectroscopy, it still finds application where spectroscopic analysis is difficult[6]. Under less severe conditions tertiary C—H bonds yield tertiary alcohols, and a high degree of stereospecificity has been observed, as exemplified by the oxidation of 3-methylheptane[7], which occurs with 70—85% retention of configuration.



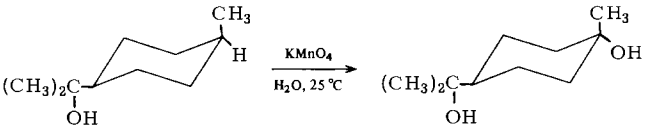
The rate of oxidation of paraffins is largely independent of structure. Steric hindrance only affects rates in highly shielded branched hydrocarbons such as 2,2,4-trimethylpentane[8], while from a study of various alkyl-substituted cyclohexanes steric acceleration was shown to play no role[9]. The relative rates of oxidation of primary : secondary : tertiary hydrogen atoms in $CH_3:CH_2:CH$ were determined as 1:114:7000–18000, and it was proposed[8] that the rate determining step involved hydride anion transfer from the hydrocarbon to the chromium(VI) complex. An alternative explanation involved the intermediacy of a radical and chromium(V) species. However, the reaction is perhaps best regarded as proceeding *via* the intermediacy of a resonance hybrid of these two complexes[9] (Scheme 1).

Scheme 1



1.2. Permanganate Oxidations

Permanganate solutions have also been extensively used as oxidizing agents[2], but they do not react like chromic acid with alkanes. For the oxidation of (4-methylcyclohexyl)-2-propanol in alkaline permanganate solution it appears that the tertiary hydroxyl group of the starting material is essential for reaction[10].



1.3. Lead(IV) Oxidations

Lead(IV) compounds have also been used for oxidizing alkanes. Thus heptane on treatment with lead(IV) trifluoroacetate is converted in 45±10% yield into trifluoroacetic acid esters[11], whilst lead(IV) acetate in trifluoroacetic acid/dichloromethane readily oxidizes bridgehead hydrocarbons[12]. With the latter reagent 94% 1-adamantanol was obtained from adamantane, after hydrolysis of the initially formed ester.

1.4. Cobalt(III) Oxidations

Cobalt(III) compounds have also been shown capable of functionalizing alkanes. Although cobalt(III) acetate in acetic acid is only slowly reduced in the presence of heptane, addition of a stronger organic or inorganic acid to the system causes rapid reduction of the cobalt(III) ion with concomitant oxidation of the alkane substrate. The products obtained from this reaction are different according to whether oxygen is

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present or not. Under nitrogen, acetic esters of heptanols are formed, whereas ketones are the principal products if oxygen is present[13].

Table 1. Oxidation of heptane with $Co(OAc)_3/HOAc/H_2SO_4$; attack at C-1, C-2, C-3, or C-4.

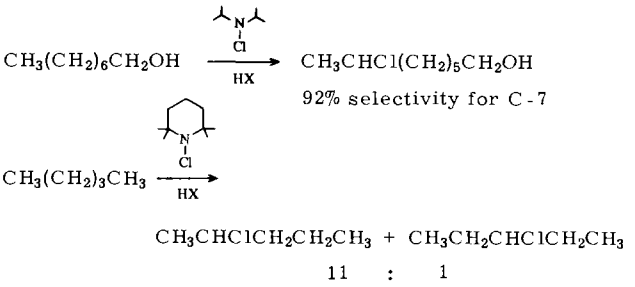
Atmosphere	Yield	Isomer Distribution			
		C-1	C-2	C-3	C-4
N_2	69% acetates	0	64	27	9
O_2	69% ketones	0	60	27	13

The mechanism is believed to involve initial attack by cobalt(III) on the alkane to give reversibly cobalt(II) and an alkyl radical. Cobalt(III) was quantitatively reduced to cobalt(II) within 23 hours at 30°C. However, only 1/3 equivalent of oxidized product was found[14].

$$c\text{-}C_6H_{12} + 2Co(O_2CCF_3)_3 \rightarrow c\text{-}C_6H_{11}O_2CCF_3 + 2Co(O_2CCF_3)_2 + CF_3CO_2H$$
35%

1.5. Chloramine Reactions

Highly selective free-radical chlorinations have been achieved with *N*-chloroammonium ions. The degree of selectivity can be modified by both polar and steric effects; exemples are, respectively, the reaction of 1-octanol[15] and the reaction of pentane[16].



1.6. Amine Oxide Reactions

In an analogous reaction *Deno* has successfully oxygenated alkanes using amine oxides[17]. Cyclohexane was oxidized by equimolar amounts of Et_2NOH or Et_3NO in trifluoroacetic acid in the presence of iron(II) ions. Cyclohexyltrifluoroacetate was isolated as the sole reaction product (25% yield). Both polar and stereoselectivity effects are observed. Thus, oxidation of octyltrifluoroacetate with Et_2NOH gave 10% of bis-esters, with oxidation at C-7 accounting for 72% of the product distribution illustrating the polar effect. Selectivity for C-7 was greater with Et_3NO, thus demonstrating the steric effect. A reaction mechanism was proposed in which an alkyl radical is converted into the ester product *via* an encumbered carbonium ion formed by Fe(III) oxidation (Scheme 2).

Scheme 2

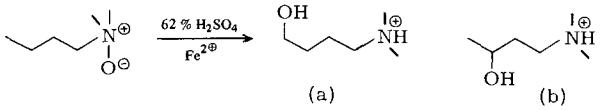
$$R_3NOH^{\oplus} + Fe^{2\oplus} \rightarrow Fe^{3\oplus} + R_3N^{\bullet\oplus} + OH^{\ominus}$$

$$R_3N^{\bullet\oplus} + R'H \rightarrow R_3NH^{\oplus} + R'^{\bullet}$$

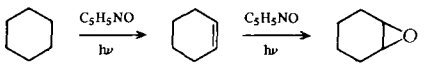
$$R'^{\bullet} + Fe^{3\oplus} \rightarrow Fe^{2\oplus} + R'^{\oplus}$$

$$R'^{\oplus} + CF_3CO_2H \rightarrow CF_3CO_2R' + H^{\oplus}$$

Presumably the intermediate carbonium ions are encumbered, either by solvent relaxation during formation or by a Fe—R^+ interaction. It was argued that such an encumbered carbonium ion would account for *Norman*'s observation of a primary alcohol (a) in the reaction[18]; a free carbonium ion would lead to total rearrangement to the secondary alcohol (b).



Another example of an amine oxide oxidation is the photolysis of pyridine-*N*-oxide in the presence of cyclohexane[19]. Interestingly, the initial step involves a dehydrogenation of cyclohexane to cyclohexene and is followed by epoxidation.



Parallels between these radical/carbocation oxidations and enzymic oxidations have been drawn and an excellent review discussing this topic has been published[20].

1.7. Electrochemical Oxidations

In recent years a new area of study for alkane oxidation—the electrochemical oxidation—has evolved, and has rapidly developed into a potentially very useful synthetic technique. *Fleischmann* and *Pletcher* found by using tetrafluoroborates or hexafluorophosphates as inert electrolytes, instead of more common salts, that it was possible to extend the electrochemical potential range in acetonitrile; at the anodic limit this enabled the study of aliphatic hydrocarbons containing weak (*e.g.* tertiary) C—H bonds[21]. They proposed the following reaction path:

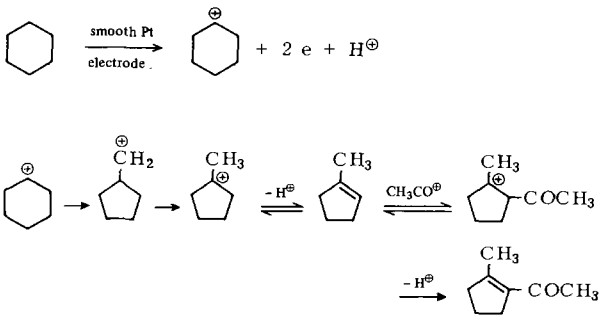
$$RH \rightarrow R^{\oplus} + H^{\oplus} + 2\,e$$

$$R^{\oplus} + CH_3CN \rightarrow CH_3\overset{\oplus}{C}{=}N{-}R \xrightarrow{H_2O} CH_3CONHR + H^{\oplus}$$

Use of fluorosulfuric acid as a solvent medium extended the range of C—H bonds that could be oxidized[22]. With a smooth platinum anode in fluorosulfuric acid which was 1 M in acetic acid, alkanes with more than four carbon atoms could be oxidized. From this reaction α,β-unsaturated ketones containing an additional two carbon atoms (derived from the acetic acid) were obtained. From cyclohexane, the α,β-unsaturated methyl(2-methyl-1-cyclopentenyl)ketone was recovered in *ca.* 30% yield (Scheme 3).

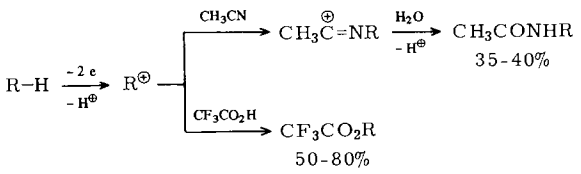
Scheme 3

$$CH_3CO_2H + FSO_3H \rightarrow CH_3CO^{\oplus} + FSO_3^{\ominus} + H_2O$$

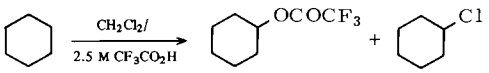


It was subsequently shown that by adding less base (acetic acid is readily protonated and hence a strong base in FSO_3H) the anodic oxidation of butane, propane and ethane became possible[23]. In stronger acid solutions, however, alkanes were found to undergo spontaneous chemical reactions yielding identical products as the electrode reactions, providing acetyl cations were present in solution. It was suggested that carbenium ions were initially formed *via* protolysis. An alternative, of course, would be electrophilic insertion of the acetyl cation into a C—H σ bond.

Electrochemical oxidation of the *n*-alkanes pentane to octane has been achieved at a smooth platinum anode in acetonitrile or trifluoroacetic acid containing a tetraalkylammonium tetrafluoroborate as electrolyte[24]. The following reaction sequences were realized.



Interestingly, in trifluoroacetic acid, cyclohexane gave cyclohexyl trifluoroacetate, in contrast to the ring contracted product obtained in FSO_3H (Scheme 3). *Fritz* and *Würminghausen*[25] likewise obtained a cyclohexyl ester.



Furthermore, these workers found that the isomer distribution observed from the electrochemical oxidation of *n*-decane in CH_2Cl_2/CF_3CO_2H solution paralleled the calculated differences in reactivity of the various methylene groups, thus indicating the participation of free carbocations.

From studies so far carried out in this area it would appear that the electrochemical oxidation of alkanes as a preparative route has an interesting and potentially useful future.

1.8. Autoxidations

The reaction of alkanes with molecular oxygen has been widely studied[26]. A representative reaction of this type is the autoxidation of isobutane in the presence of hydrogen bromide at 158 °C giving di-*tert*-butyl peroxide as the major product together with *tert*-butyl alcohol and isobutyraldehyde. High yields of *tert*-butyl hydroperoxide (75 %) could also be obtained[27]. The mechanism shown in Scheme 4 was proposed.

Scheme 4

$$HBr + O_2 \longrightarrow Br\bullet + HOO\bullet$$

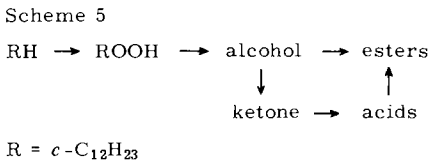
$$CH(CH_3)_3 + Br\bullet \longrightarrow \bullet C(CH_3)_3 + HBr$$

$$\bullet C(CH_3)_3 + O_2 \longrightarrow (CH_3)_3COO\bullet$$

$$(CH_3)_3COO\bullet + HBr \longrightarrow (CH_3)_3COOH + Br\bullet$$

For cyclododecane it has been shown by kinetic studies that the cycle illustrated in Scheme 5 is operative[28].

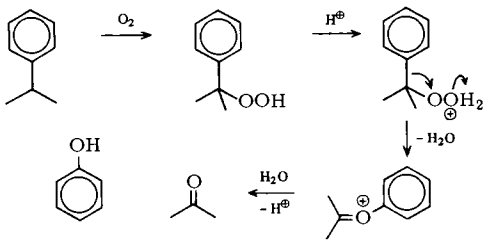
Scheme 5



R = c-$C_{12}H_{23}$

The most important example of this type of reaction is the oxidation of cumene to cumene hydroperoxide. Originally discovered by *Hock* and *Lang*[29] it forms the basis of the industrial production of phenol and acetone *via* the acid-catalyzed decomposition of the hydroperoxide (Scheme 6). As might be expected the industrial importance of this reaction has stimulated much research towards increasing the efficiency of the overall process. Much of this work is described in the patent literature and some of these developments have been discussed in a review by *Hock*[30].

Scheme 6



The intermediary dimethylphenylcarboxonium ion has recently been characterized by NMR spectroscopy[31]. It was prepared by treating cumyl peroxyacetate with magic acid in SO_2ClF solution at −78 °C.

Other important examples of industrial autoxidation processes are the oxidation of *p*-xylene to terephthalic acid, an intermediate in the synthesis of terylene[32], and the oxidation of cyclohexane[33] to a mixture of cyclohexanol and cyclohexanone. This mixture is then further oxidized by nitric acid to adipic acid, which is an intermediate in the production of nylon.

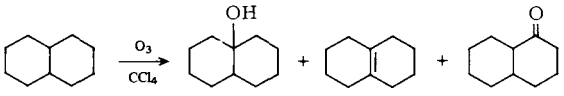
A major problem in the autoxidation (and indeed in all other oxidations) of alkanes is that the initial products of oxidation—alcohols, ketones, *etc.*—are often more easily oxidized further than is the starting alkane itself. This problem has been alleviated by the use of boric acid additives which tend to give products with enhanced alcohol content. *Illingworth* and *Lester*[34] found that by using boric acid, at a conversion of 15 %, *n*-dodecane gave a product having an alcohol/ketone ratio of 9:1, whereas without boric acid a ratio of 1:1 was obtained. The authors proposed that the boric acid captured the initially formed hydroperoxide and the intermediates were then converted into *sec*-alkyl borates.

As with many important industrial discoveries, an understanding of the mechanistic aspects of autoxidation lagged behind the commercialization of the processes. Efforts towards identification of the initial state of attack by oxygen on long-chain hydrocarbons illustrate this point. Early work suggested oxidation occurred at the terminus of the chains[35], whilst from a study of the oxidation of *n*-heptane it was thought that attack took place preferentially at the 2-position[36]. From experiments on the oxidation of *n*-decane *Leibnitz et al.*[37] concluded that attack was either at the 1- or 3-position. This

rather uncertain state of affairs was given a sounder footing during the 1950's[38]. It was shown that in fact oxidation of *n*-decane yielded the isomeric 2-, 3-, 4- and 5-decanols in approximately equimolar amounts, whilst only trace amounts of the 1-decanol was detected, indicating that initial attack occurs at all positions in the chain, with only minor reaction occurring at the terminus.

1.9. Ozone Oxidations

The action of ozone towards unsaturated hydrocarbons has long been employed as a means of functionalization, and the subject has been extensively reviewed. In contrast, the reaction of ozone towards saturated hydrocarbons has received scant attention. Early work showed that ozone reacted with alkanes, though the results were not encouraging in terms of synthetic usefulness. For example, it was found that *cis*-decalin reacted more rapidly than *trans*-decalin and that, under controlled conditions, the *cis* isomer gave as principle isolated products 4a-decalol, 1,2,3,4,5,6,7,8-octahydronaphthalene and some 1-decalone, whereas the *trans*-isomer yielded only 4a-decalol and 1-decalone. The reaction also produced large amounts of uncharacterized material thought to be carboxylic acids[39].

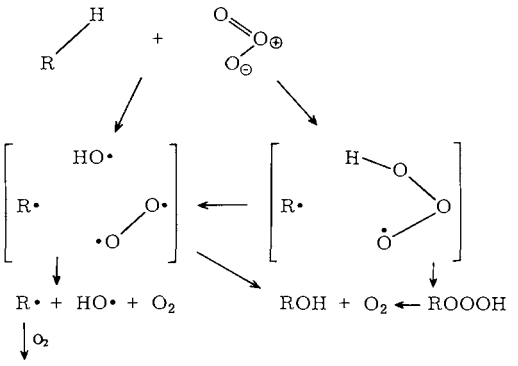


Reports since the work of *Durland* and *Adkins*[39] have mostly dealt with mechanistic aspects of the ozonolysis of C—H bonds. *Schubert* and *Pease*[40] studied the gas-phase ozonization of methane, propane, butane, and isobutane and determined the second order rate constants, which they found to depend on the strength of the C—H bond. Isobutane with a tertiary C—H bond showed a 14-fold rate increase and a fall in activation energy from 14.9→10.3 kcal/mol over methane, which has only primary C—H bonds. However, in subsequent work the same group[41,42] observed that there was no difference in activation energies from the ozonization of methane, ethane, and propane, and that ethane with only primary C—H's exhibited a greater reactivity than propane, which has two secondary C—H bonds.

Williamson and *Cvetanović*[43] examined the ozonolysis of alkanes in carbon tetrachloride solution, and found the reactivity to be similar to that of benzene, with comparable rate constants to those for ozonolysis in the gas phase.

Hamilton et al.[44] deduced from the liquid-phase ozonolysis of isopentane, that the relative reactivities of primary : secondary : tertiary hydrogens are approximately 1 : 13 : 110. Comparing these ratios with those obtained for chromate oxidations of alkanes (1 : 110 : 7000, see Section 1.1) it is apparent that the transition state for alkane ozonization cannot have a great deal of carbenium ion character. However, ozonization of tertiary C—H's to tertiary alcohols gave 60—70% retention of configuration, which is inconsistent with the usual observations for free radical mechanisms. A mechanism was proposed in which the initial step is an insertion reaction, the transition state of which has considerable radical character. It was suggested that the observed retention of configuration could be explained by a solvent caged radical intermediate(s) (Scheme 7).

Scheme 7



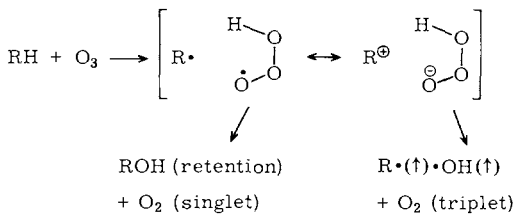
ROH (racemized; + ketone + peroxides + fragmentation products)

From consideration of bond strengths *Benson*[45] estimated that the reaction

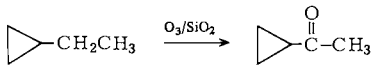
$$RH + O_3 \rightarrow R\cdot + \cdot OOOH$$

is endothermic by at least 20 kcal/mol and concluded that an ion pair mechanism for alkane ozonolysis could not be ruled out. *Hamilton*[46] has revised his mechanism to allow for some degree of ionic character in the transition state (Scheme 8).

Scheme 8



More recently, synthetically useful ozonizations have been reported. These have been achieved by *Mazur et al.*[47] using a dry ozonization method, which involves presorbing the alkane on silica gel followed by passing a stream of ozone over the bed at −78 °C until it becomes saturated with ozone[47]. On warming to room temperature and elution of the organic material from the bed, almost quantitative conversions were obtained. From *cis*-decalin and the isomeric *cis*- and *trans*-1,4-dimethylcyclohexane, tertiary alcohols were formed with almost complete retention of configuration[48]. The dry ozonization technique has been successfully used for the oxidation of alkylcyclopropanes in the α-position to the cyclopropyl group[49].



95%

The selectivities found for reactions utilizing the dry ozonization method makes it a promising tool for future synthetic work.

2. Superacid Catalyzed Oxygenations

The discovery and development of highly acidic and weakly nucleophilic solvents such as FSO_3H-SbF_5-SO_2[*], FSO_3H-SbF_5-SO_2ClF[*] and HF-SbF_5-SO_2ClF has enabled the prep-

[*] FSO_3H-SbF_5 is known as "magic acid".

aration and study of a wide variety of carbocations[50]. Furthermore, by using the above solvent systems as reaction media the chemistry of alkanes has been greatly extended[50, 51].

In connection with these studies it was also found that the electrophilic oxygenation of alkanes with ozone and hydrogen peroxide takes place readily in the presence of superacid media under typical electrophilic conditions. The reactions, giving oxyfunctionalized products, can be explained as proceeding *via* initial electrophilic attack by protonated ozone, *i.e.* HO_3^+, and the hydroperoxonium ion, $H_3O_2^+$, respectively, on the σ-bonds of alkanes through pentacoordinated carbonium ions. (It is suggested, to differentiate conventional "oxidations" from acid catalyzed electrophilic "oxygenations".)

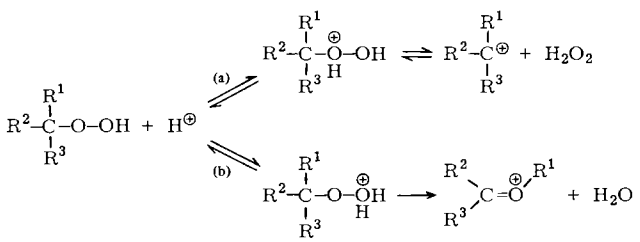
The study of the superacid catalyzed oxygenation reactions, was initiated by investigations of the acid induced decomposition of a series of peroxy compounds. Characterization of the reaction paths and intermediates of these reactions in superacidic media by NMR spectroscopy enabled the elucidation of the mechanism of the superacid induced electrophilic oxygenation of saturated hydrocarbons and allowed subsequent development of direct oxygenation methods for alkanes.

2.1. Protolytic Cleavage of Peroxy Compounds

2.1.1. Hydroperoxides

Consideration that superacid media would allow the direct observation of the intermediates involved in the acid-induced decomposition of hydroperoxides called for investigation of the reaction of a series of *tert*-alkyl hydroperoxides with magic acid-SO_2ClF solution. As shown in Scheme 9, initial protonation can occur at either oxygen of the hydroperoxide[52].

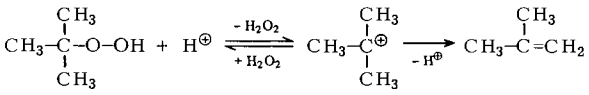
Scheme 9



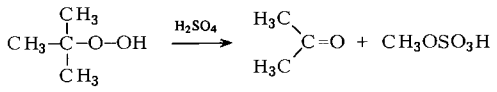
Reaction *via* route (a) would lead to an overall equilibrium between the precursor hydroperoxide and its corresponding carbenium ion. Indeed, such an equilibrium has been found to interfere with kinetic studies of the acid induced rearrangement reaction of a number of aryl- and alkaryl hydroperoxides[53], *i.e.* the rearrangement shown as route (b), resulting in irreversible formation of the corresponding carboxonium ion. The relative migratory aptitude of the migrating group R, shows the following trend[54]:

phenyl > vinyl > cyclopentyl > propyl > ethyl ≫ methyl
hydrogen ≈ propyl

The investigation of hydroperoxides centered on that of *tert*-butyl hydroperoxide since this compound is readily available commercially. Previous workers had found it to be remarkably resistant towards rearrangement in the presence of acid. When treated with sulfuric or perchloric acid in acetic acid it failed to undergo rearrangement. Instead, C—O cleavage occurred [route (a), Scheme 9] resulting in formation of isobutene and hydrogen peroxide[55].

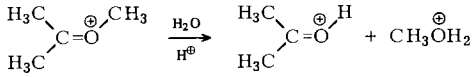


On the other hand, reaction *via* O—O cleavage [route (b), Scheme 9] occurred exclusively when *tert*-butyl hydroperoxide was treated with 90—98 % sulfuric acid at −25 °C[56].



These findings indicate that the acid concentration determines the course of reaction taken[52]. Indeed, spectroscopic analysis of the solution obtained when *tert*-butyl hydroperoxide was allowed to react with a twofold excess of magic acid-SO_2ClF at −78 °C showed the products to be consistent with exclusive reaction *via* O—O cleavage, the major species identified by ^{13}C- and ^1H-NMR being the dimethylmethylcarboxonium ion. However, water liberated from the hydroperoxide caused some hydrolysis of the carboxonium ion, indicated by the presence of acetone and methanol as minor species.

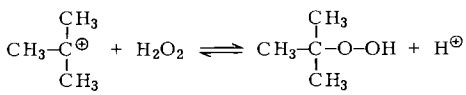
Scheme 10



Similar treatment of *tert*-butyl hydroperoxide with a fivefold excess of magic acid again gave the carboxonium ion as the dominant species (85 %) *via* O—O bond cleavage. However, a significant amount (15 %) of the trimethylcarbenium ion was also formed, thus indicating some reaction *via* C—O cleavage (cf. Scheme 9, route (a)).

It was concluded from the observation of both mechanistic pathways in a strong acid medium that the nucleophilicity of the liberated hydrogen peroxide is reduced by protonation, thus preventing the reverse reaction formulated in Scheme 11.

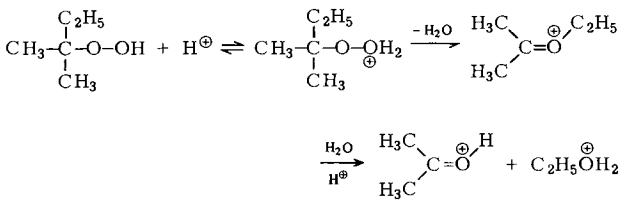
Scheme 11



The large excess of acid is necessary for effective protonation of the hydrogen peroxide[57].

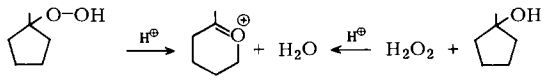
On treatment of *tert*-alkyl hydroperoxides other than *tert*-butyl hydroperoxide with a fivefold excess of magic acid, no species due to C—O cleavage could be detected. All observable products being accounted for by the O—O cleavage route, as exemplified for the case of *tert*-pentyl hydroperoxide (Scheme 12).

Scheme 12



The same results were also obtained with alkyl hydroperoxides generated *in situ*. Thus, treatment of 1-methyl-1-cyclopentanol and hydrogen peroxide with magic acid yielded the same cyclic carboxonium ion as 1-methylcyclopentylhydroperoxide (Scheme 13).

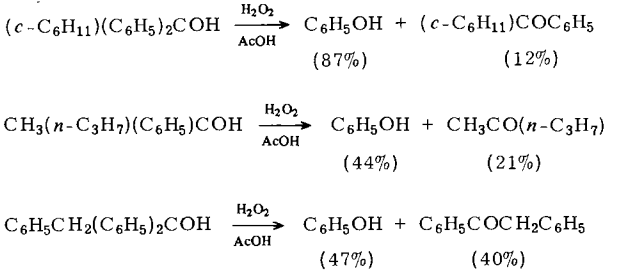
Scheme 13



NMR spectroscopy was found to be a most convenient method for the analysis of the carboxonium ions thus obtained. ^{13}C-NMR parameters of typical carboxonium ions are shown in Table 2.

if one of the products was stable towards the reaction medium. Thus, for example, in the reaction of cumyl alcohol with

Scheme 14



hydrogen peroxide/magic acid (or FSO_3H) acetone was detected as a product (Scheme 15).

Scheme 15

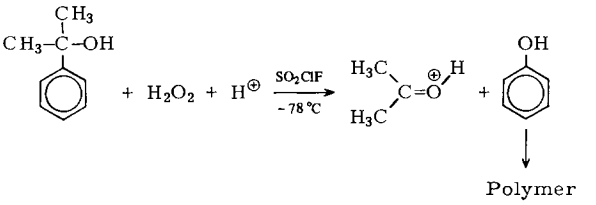
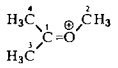
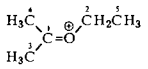
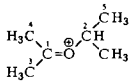
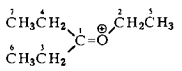
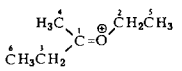
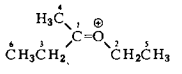


Table 2. ^{13}C-NMR parameters of some intermediary carboxonium ions (in SO_2ClF, TMS ext., −40°C).

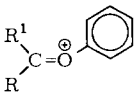
Structure	δ(^{13}C) 1	2	3	4	5	6	7
	245.21	68.81	32.2	27.01			
	243.13	82.47	32.37	27.27	13.03		
	240.72	95.09	32.68	26.72	20.76		
	247.92	80.74	34.3	28.72	13.04	11.03	8.05
	241.8	84.63	37.73	30.17	20.46	14.72	
	248.61	87.35	40.24	32.83	28.38	25.23	21.49
	243.64	81.57	39.86	25.27	12.05	5.25	
	246.57	80.52	33.80	28.70	12.05	7.49	

2.1.2. Arylalkyl Hydroperoxides

The reactivity of some α-arylalkyl alcohols with hydrogen peroxide/magic acid has also been studied[58]. *Kharasch* had previously found that hydrogen peroxide/acetic acid was able to induce aryl group migration in arylalkyl alcohols *via* their hydroperoxides[59] (Scheme 14).

No intermediates were characterized from this study. Hydrogen peroxide/magic acid was found to be too powerful a reagent for arylalkyl alcohols, the reactions yielding polymeric materials. However, the course of reaction could be ascertained

Polymerization of phenol is induced by the excess hydrogen peroxide. Hydrogen peroxide in the presence of strong acid is an extremely powerful electrophilic hydroxylating agent (cf. Sections 2.2 and 2.3 and also [60]). No polymerization was observed on reacting the corresponding hydroperoxides with magic acid. Cumyl hydroperoxide, for example, gave protonated phenol and acetone (see Scheme 6). The intermediary carboxonium ions, however, could not be observed on starting from the hydroperoxides, as ions of this type appear extremely susceptible towards hydrolysis.

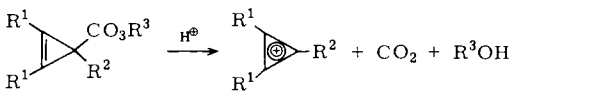


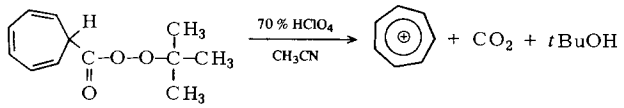
However, these intermediates may be obtained from aryl-alkyl peroxy esters.

2.1.3. Peroxy Esters

The acid induced decomposition of a series of *tert*-alkyl peroxyacetates in superacid media was studied in order to gain a better understanding of the mechanism of the reaction discussed in Section 2.1.2 by observation of the intermediary carboxonium ions.

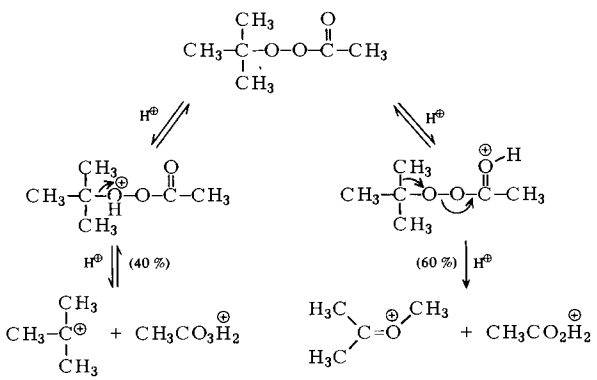
Protolytic cleavage of peroxy esters has previously been used for the preparation of stable carbocations. For example, cyclopropeneperoxycarboxylates yielded the corresponding cyclopropenylium ion, whilst the tropylium ion was obtained from the corresponding cycloheptatrienyl peroxy ester[61].



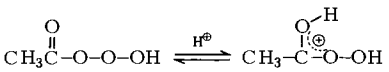


Recent studies[31] revealed that treatment of simple peroxy esters, such as *tert*-butyl or *tert*-pentyl peroxyacetates in superacids gave results similar to those of the corresponding hydroperoxides. Thus *tert*-butyl peroxyacetate reacts with a fivefold excess of magic acid as outlined in Scheme 16.

Scheme 16



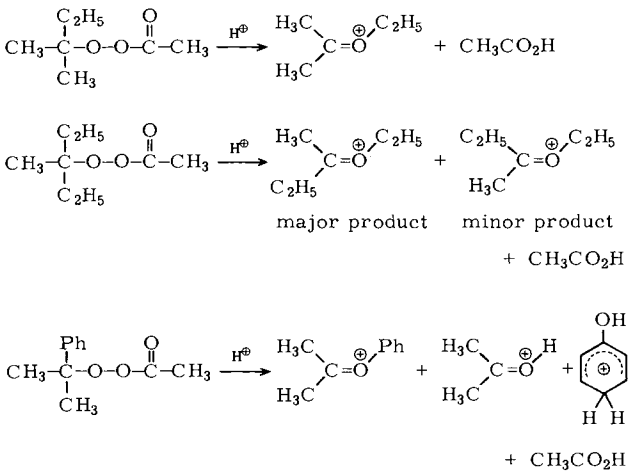
As in the case of *tert*-butyl hydroperoxide both O—O and C—O cleavage was observed. As expected in the reaction with a twofold excess of magic acid only O—O cleavage was observable. The formation of the trimethylcarbenium ion in the former case is due to the deactivation of the liberated peroxyacetic acid as a nucleophile by its protonation.



This reaction was shown to be reversible; warming of the reaction mixture from −78 to −10°C resulted in complete disappearance of the *tert*-butyl cation, leaving the O—O cleavage products as the only observable species in solution.

When *tert*-alkyl peroxyacetates other than *tert*-butyl peroxyacetate were treated with a fivefold excess of magic acid the only observable products were those due to O—O cleavage (Scheme 17).

Scheme 17



The stability of the carbenium ion formed as a result of C—O cleavage is not an important factor in determining the course of reaction. This is demonstrated by the fact that only O—O cleavage products were observed in the decomposition of cumyl peroxyacetate. Had the carbenium ion stability had a significant effect, then the dimethylphenylcarbenium ion, which is more stable than the trimethylcarbenium ion[62], should have been observed.

It was concluded that the carbenium ion formed as one of the decomposition products of peroxy esters is generally dependent on the rate of protolytic deactivation of peroxyacetic acid, formed *via* C—O cleavage, being greater than the rate of alkyl group migration following O—O cleavage. Only in the case of *tert*-butyl peroxyacetate (*i.e.* methyl migration) is this not the observed pattern.

The reaction of cumyl peroxyacetate with magic acid allowed direct observation of the dimethylphenylcarboxonium ion. This ion has long been proposed as the key intermediate in the industrially important conversion of cumene hydroperoxide into acetone and phenol[63].

Table 3. Products of the reaction of *tert*-butyl peroxy esters with magic acid [a]

$(CH_3)_3C-O-O-CO-R \rightarrow$

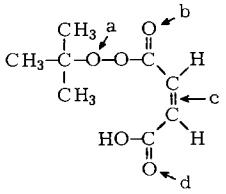
$(CH_3)_2C{=}O{-}CH_3$ (*1*) + $(+(CH_3)_3C^{\ominus})$ (*2*) + ···

Peroxy ester R	% O—O Cleavage	% C—O Cleavage	Products
CH_3	60	40	(*1*), (*2*), acetic acid, peracetic acid
C_6H_5	85	15	(*1*), (*2*), benzoic acid, perbenzoic acid
H	>95	<5	(*1*), (*2*), formic acid
cis-CH=CH—COOH	>95	<5	(*1*), (*2*), maleic acid, fumaric acid
α-Pyridyl	100	0	(*1*), α-picolinic acid

[a] All reactions with fivefold excess of magic acid in SO_2ClF at −78°C.

Attempts to observe dimethylphenylcarboxonium ions by reacting cumene hydroperoxide in superacids failed[58]. Only protonated acetone and phenol were detected, reflecting the ease with which the ion is susceptible to hydrolysis.

In the study of a series of *tert*-butyl peroxy esters it was shown that the extent of C—O cleavage was dependent on the pK_a of the acylperoxy leaving group (see Table 3) and the number of additional sites available for initial protonation, *i.e.* sites other than the peroxy ester oxygen atoms, as for



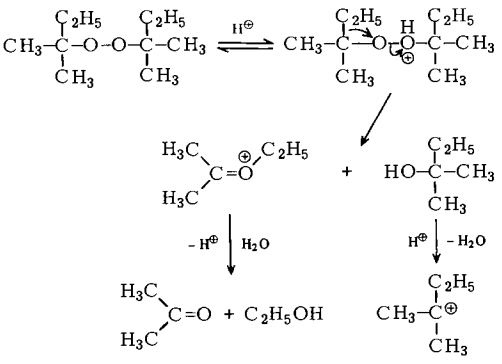
example in the case of *tert*-butyl peroxymaleate. Protonation at (a) leads to C—O cleavage, at (b), (c) and (d) to O—O cleavage.

2.1.4. Dialkyl Peroxides

Another class of peroxy compounds studied under superacidic conditions was the dialkyl peroxides. Although these compounds have been the subject of extensive research in homolytic decompositions[64] there has previously been little or no data available on their behavior in acidic media.

The solutions obtained upon treating dialkyl peroxides with magic acid[65], unlike in the case of their hydroperoxide counterparts, always showed the presence of alkylcarbenium ions as reaction products. However, this did not arise from a C—O cleavage, but rather from ionization of the alcohols produced as a result of O—O cleavage. This is illustrated in Scheme 18 showing the reaction of di-*tert*-pentyl peroxide with magic acid.

Scheme 18

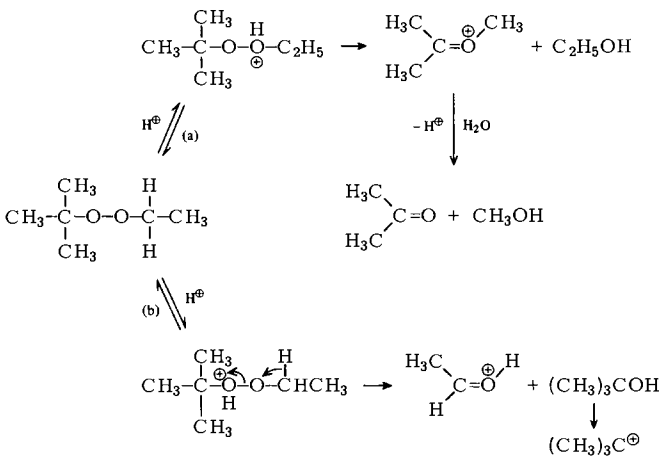


Analogous results were obtained with di-*tert*-butyl peroxide and dicumyl peroxide.

An interesting feature of dialkyl peroxides is that they also can be obtained with dissimilar alkyl groups. The two oxygen atoms are now in differing environments. Thus, initial protonation is influenced by the relative difference in steric crowding and/or the basicity of each oxygen.

The result of the reaction of *tert*-butylethyl peroxide as shown in Scheme 19 seems somewhat surprising, since one might expect the reaction path (b) to be preferred, hydrogen being a much better migrating group than methyl. However,

Scheme 19



examination of molecular models shows that the oxygen adjacent to the ethyl group is sterically less shielded, consequently it is this oxygen atom that is preferentially protonated (path (a)).

2.2. Baeyer-Villiger Oxidation in Strong Acids

The Baeyer-Villiger oxidation of ketones is generally not applicable to methyl alkyl ketones.

Hudlecky reported the first example of a Baeyer-Villiger oxidation of methyl alkyl ketones with hydrogen peroxide in hydrofluoric acid[66]. More recently, *Deno et al.* observed that solutions of $K_2S_2O_8$ in 50% sulfuric acid gave quantitative yields of the Baeyer-Villiger products for simple aliphatic ketones[56]. In these examples, the reaction was generally carried out at a temperature of 10—40 °C, and products arose exclusively from migration of the ethyl, propyl or higher alkyl groups rather than methyl.

Subsequently, FSO_3H-H_2O_2 was found to be an extremely effective reagent for the oxidation of simple methyl ketones even at −40 °C or below[67]. The results obtained for a number of ketones are summarized in Table 4.

Table 4. Baeyer-Villiger oxidation of aliphatic ketones [a].

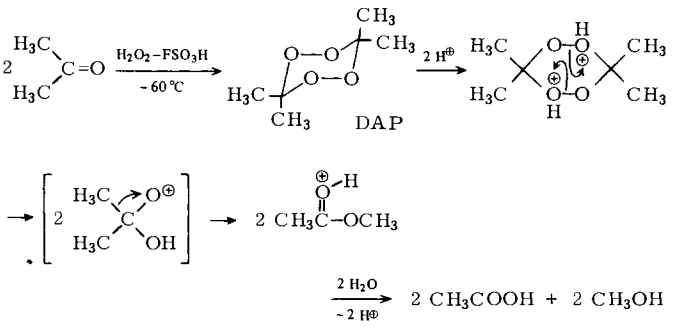
Ketone	Products [b]
2-Butanone	$CH_3CO—OC_2H_5$ [c]
2-Pentanone	$CH_3CO—OC_3H_7$ [c]
3-Pentanone	$C_2H_5CO—OC_3H_7$ [c]
2-Hexanone	$CH_3CO—OC_4H_9$ [d]
2-Heptanone	$CH_3CO—OC_5H_{11}$ [d]
4-Heptanone	$C_3H_7CO—OC_3H_7$ [c]

[a] Ketone/FSO_3H/H_2O_2/SO_2ClF, −40 °C. [b] Determined by ^{1}H-NMR spectroscopy. [c] For ketone:H_2O_2 = 1:2; 60% conversion. [d] For ketone:H_2O_2 = 1:5; quantitative conversion.

Because of the great difficulty of methyl migration, there has been no previous report on the Baeyer-Villiger oxidation of acetone. However, it was found that even acetone reacts with hydrogen peroxide in FSO_3H giving Baeyer-Villiger oxidation products[68].

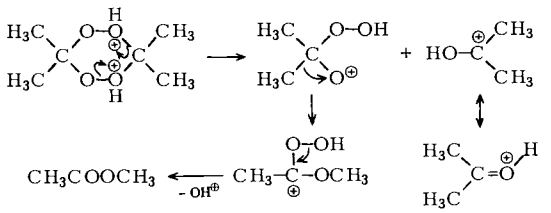
With acetone in excess FSO_3H-hydrogen peroxide solution no reaction was observed at −78 °C, but on raising the temperature to −60 °C, ^{1}H-NMR spectroscopy showed the appearance of the axial and equatorial methyl groups of dimeric acetone peroxide (3,3,6,6-tetramethyl-1,2,4,5-tetraoxane,

Scheme 20



"DAP"). At −20°C, conversion of acetone to this compound was almost complete.

Scheme 21



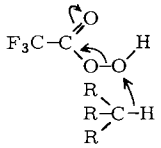
Formation of dimeric acetone peroxide was confirmed by comparison of the spectra of an authentic sample (synthesized by the method of *Criegee*[69] and of *Sanderson*[70]) and the spectra of the reaction products in strong acid.

On allowing the solution to stand at room temperature, the formation of methyl acetate, methyl alcohol, acetic acid, as well acetone was observed. The first three of these are Baeyer-Villiger oxidation products (as shown in Scheme 20). The formation of acetone can be depicted as shown in Scheme 21.

2.3. Electrophilic Oxygenation of Alkanes with Hydrogen Peroxide in Superacids

Previously reported hydroxylation reactions of hydrocarbons with hydrogen peroxide in acid solution were mainly those of π-donor systems, such as aromatic hydrocarbons[71] and alkenes[72].

The reaction of alkanes with 85% hydrogen peroxide in hydrogen fluoride/boron trifluoride was first observed by *Alder* and *Whiting* to be exceptionally destructive and unselective[71d]. On the other hand, *Frommer* and *Ullrich* reported that the hydroxylation of alkanes with 85% hydrogen peroxide in the presence of trifluoroacetic acid at 20°C gives the corresponding alcohols[73]. They suggested a nonionic transition state to be involved in the course of the reaction. *Deno et al.* have recently studied in detail the hydroxylation of alkanes with 30% hydrogen peroxide in trifluoroacetic acid. Good yields of alcohols were obtained without further oxidation to ketones.



Hamilton et al. also observed that oxidation of cyclohexane and 1,2-dimethylcyclohexane with peracetic acid gives the corresponding alcohols[74].

As mentioned above, and also suggested by *Alder* and *Whiting*[71d], hydrogen peroxide is expected to be protonated in strong acids, giving the hydroperoxonium ion, *i.e.* $H_3O_2^+$. In superacids the protonation equilibrium is expected to be substantially on the side of the hydroperoxonium ion. This ion may be considered to be effective enough for the electrophilic hydroxylation of single (σ-) bonds in alkanes, and thus be able to effect reactions similar to such electrophilic reactions as hydrogen/deuterium exchange, protolysis[75], chlorination (chlorolysis)[76] and nitration (nitrolysis)[77].

2.3.1. Branched Chain Alkanes

The reaction of branched chain alkanes with hydrogen peroxide in magic acid-SO_2ClF solution was carried out with various ratios of alkane and hydrogen peroxide, and at different temperatures[68]. Some of the results are summarized in Table 5.

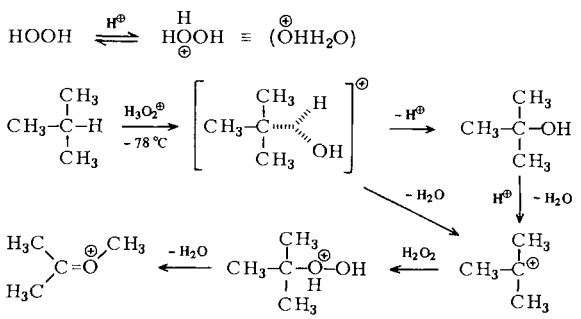
Table 5. Products of the reaction of branched chain alkanes with H_2O_2 in magic acid-SO_2ClF solution [a].

Alkane	Alkane [mmol]	H_2O_2 [mmol]	Temp. [b] [°C]	Major Products
	2	2	−78 → −20	$(CH_3)_2C{=}\dot{O}CH_3$
	2	4	−78 → −20	$(CH_3)_2C{=}\dot{O}CH_3$
	2	6	−78 → −20	$(CH_3)_2C{=}\dot{O}CH_3$
	2	6	+20 [c]	$(CH_3)_2C{=}\dot{O}CH_3$ (trace), DAP [d] (25%), CH_3OH (50%), $CH_3CO{-}O{-}CH_3$ (25%)
	2	3	−78 → −20	$(CH_3)_2C{=}\dot{O}C_2H_5$, $C_2H_5(CH_3)_2C^{\oplus}$
	2	6	−78 → −20	$(CH_3)_2C{=}\dot{O}C_2H_5$
	2	4	−78	$(CH_3)_2C{=}\dot{O}CH_3$ (50%), $(CH_3)_2C{=}OH$ (50%)
	2	6	−40	$(CH_3)_2C{=}\dot{O}CH_3$ (50%), DAP [d] (50%)

[a] All experiments were carried out using a solution of 1 ml magic acid in 1 ml SO_2ClF. The resultant solutions were transferred to precooled NMR tubes for analysis. [b] NMR probe temperature. [c] The ratio of these products can be determined by using the characteristic ^{1}H-NMR signals of the methyl groups (separate singlets). [d] "Dimeric acetone peroxide" (see Scheme 20).

As neither hydrogen peroxide nor magic acid-SO_2ClF alone led to any reaction under the conditions employed, the reaction must be considered to proceed *via* electrophilic hydroxylation. Protonated hydrogen peroxide inserts into the C—H bond of an alkane. A typical reaction path is as depicted in Scheme 22. The reaction proceeds *via* a pentacoordinate hydrooxycarbonium ion transition state, which decomposes to either *tert*-butyl alcohol or the *tert*-butyl cation. Since 1 mol of isobutane requires 2 mol of hydrogen peroxide to complete reaction one can conclude that intermediate alcohol or carbocation reacts with excess hydrogen peroxide, giving *tert*-butyl hydroperoxide. The superacid induced rearrangement and

Scheme 22



cleavage of the hydroperoxide results in very rapid formation of the dimethylmethylcarboxonium ion (cf. Scheme 9a).

When the reaction was carried out at room temperature, by means of passing isobutane into a solution of magic acid and excess hydrogen peroxide, the formation of methyl alcohol, methyl acetate and some dimethylmethylcarboxonium ion together with dimeric acetone peroxide was observed. These results clearly show that the products observed can be rationalized as arising from hydrolysis of the carboxonium ion and from Baeyer-Villiger oxidation of acetone.

The reactions of alkanes with hydrogen peroxide in the presence of acids weaker than magic acid, such as FSO_3H, HF, and H_2SO_4 (96 %), have also been studied. The results are summarized in Tables 6, 7 and 8, respectively.

The products formed in the reaction using FSO_3H were almost identical with those formed in magic acid. Some of the differences observed in FSO_3H, compared to those observed under the same reaction conditions in the magic acid system, were lower conversion rate of alkanes and increased formation of products due to hydrolysis of the carboxonium ions or esters. This is due to the lower acidity of FSO_3H, which enhances the nucleophilic activity of water (the hydronium ion in equilibrium with unprotonated water increases).

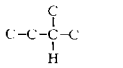
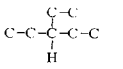
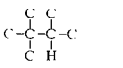
As expected, this tendency increases when the reactions are carried out in the presence of hydrogen fluoride or sulfuric acid. In order to induce the reaction of alkanes with hydrogen peroxide a temperature of at least −40 °C (or higher) is needed in the case of hydrogen fluoride and −10 °C (or higher) in the case of sulfuric acid. A constant relationship in the ratio of reaction products was observed. For example, in H_2SO_4, isobutane gave methyl alcohol and acetic acid in the molar

Table 6. Products of the reaction of branched chain alkanes with H_2O_2 in FSO_3H solution [a].

Alkane	Alkane [mmol]	H_2O_2 [mmol]	Temp. [b] [°C]	Reaction Time [min] [c]	Conversion of Alkane [%]	Products
	2	4	−78	30	10	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (100 %)
	2	4	−10	30	40	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (90 %), CH_3OH (5 %), $(CH_3)_2C{=}O$ (5 %)
	2	4	20	180	100	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (30 %), CH_3OH (35 %), $(CH_3)_2C{=}O$ (35 %)
	2	6	−78	30	25	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (100 %)
	2	6	−40	20	80	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (100 %)
	2	6	−20	60	100	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (70 %), CH_3OH (20 %), DAP [d] (10 %)
	2	6	20	60	100	$(CH_3)_2{=}\overset{\oplus}{O}CH_3$ (10 %), CH_3OH (35 %), DAP [d] (10 %), CH_3COOCH_3 (30 %), CH_3COOH (15 %)
	2	10	−78	30	5	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (100 %)
	2	10	−60	30	60	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (40 %), CH_3OH (40 %), DAP [d] (20 %)
	2	10	−40	30	100	CH_3OH (70 %), DAP [d] (30 %)
	2	20	−78	30	Tr [g]	CH_3OH (70 %), DAP [d] (30 %)
	2	20	−60	30	10	CH_3OH (70 %), DAP [d] (30 %)
	2	20	−40	30	40	CH_3OH (70 %), DAP [d] (30 %)
	2	20	0	60	100	CH_3OH (40 %), CH_3COOH (20 %), CH_3COOCH_3 (30 %), DAP [d] (10 %)
	2	4	−78	30		$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$ (100 %)
	2	4	−40	60		$(CH_3)_2C{=}O$ (50 %), C_2H_5OH (50 %)
	2	4	20	60		$(CH_3)_2C{=}O$ (50 %), C_2H_5OH (50 %)
 [e]	2	6	−78	30		$(CH_3)_2C{=}\overset{\oplus}{O}CH_2CH_3$ (70 %), C_2H_5OH (20 %), DAP [d] (10 %)
	2	6	−60	30		$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$ (25 %), C_2H_5OH (50 %), DAP [d] (25 %)
	2	6	20	60		CH_3OH (20 %), C_2H_5OH (50 %), CH_3COOCH_3 (10 %), CH_3COOH (20 %)
 [e]	2	4	−78	30		$C_2H_5C(CH_3){=}\overset{\oplus}{O}C_2H_5C_2H_5OH$ [f]
	2	4	−40	30		C_2H_5OH, CH_3COOH, $CH_3COOC_2H_5$ [f]
 [e]	2	4	−78	30		$(C_2H_5)_2C{=}\overset{\oplus}{O}C_2H_5$, C_2H_5OH [f]
	2	4	−40	30		$C_2H_5COOC_2H_5$ (50 %), C_2H_5OH (50 %)
 [e]	2	6	−40	30		CH_3OH (50 %), DAP [d] (50 %)

[a] Reaction procedures and analysis cf. Table 5. [b] ^{1}H-NMR probe temperature. [c] Time the sample kept at given temperature before analysis. Dimeric acetone peroxide. [e] Because of complex reaction mixture, conversion could not be ascertained. [f] Yet unidentified by-products were also observed. [g] Tr = traces.

Table 7. Products of the reaction of branched chain alkanes with H_2O_2 in HF solution [a].

Alkane	Alkane [mmol]	H_2O_2 [mmol]	Reaction Temp. [°C]	Reaction Time [min]	Conversion of Alkane [%]	Products
	2	4	−50	60		$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$
	2	4	−10	30		$(CH_3)_2C{=}O$ (50 %), CH_3OH (50 %)
	2	6	−40	30		DAP [c] (50 %), CH_3OH (50 %)
	2	6	−20	30	≈100	DAP [c] (10 %), CH_3COOCH_3 (20 %), CH_3COOH (10 %), CH_3OH (60 %)
	2	6	−40	30		DAP [c] (50 %), C_2H_5OH (50 %)
	2	6	−40	30		$(C_2H_5)_2C{=}O$ (20 %), C_2H_5OH (50 %), $C_2H_5COOC_2H_5$ (30 %)
	2	6	−10	60	≈100	CH_3OH (50 %), CH_3COOCH_3 (25 %), CH_3COOH (25 %)

[a] Reaction procedures and analysis cf. Table 5. [b] Because of poor miscibility of alkane with HF accurate conversions could not be observed in most systems. [c] Dimeric acetone peroxide.

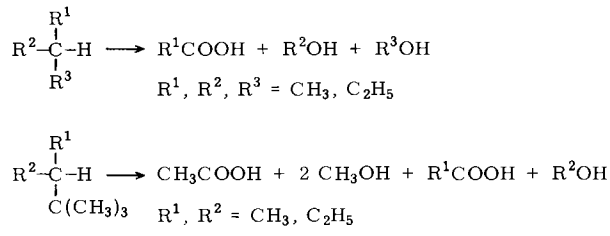
Table 8. Products of the reaction of branched chain alkanes with H_2O_2 in H_2SO_4 solution [a].

Alkane	Alkane [mmol]	H_2O_2 [mmol]	Reaction Temp. [°C]	Reaction Time [min]	Conversion of Alkane [%]	Products
 [b]	100	10	−20		0	
	100	10	0		Tr [g]	CH_3OH (70 %), CH_3COOH [d] (30 %)
	100	10	20		15 [c]	CH_3OH (70 %), CH_3COOH [d] (30 %)
	2	4	−10	30	Tr [g]	$(CH_3)_2C{=}O$ (50 %), C_2H_5OH (50 %)
	2	6	0	30	Tr [g]	CH_3COOCH_3 (50 %), C_2H_5OH [e, f] (50 %)
	2	6	20	30	≈20	C_2H_5OH [e] (40 %), CH_3OH (20 %), CH_3COOCH_3 (20 %), CH_3COOH [f] (20 %)
	2	6	40	10	≈20	CH_3OH (33 %), C_2H_5OH [e] (33 %), CH_3COOH [f] (33 %)
	2	6	0	60	≈20	CH_3OH (50 %), CH_3COOH (30 %), $(CH_3)_3COSO_3H$ [f] (20 %)
	2	6	40	60	≈20	CH_3OH (60 %), CH_3COOH [d] (40 %)

[a] Reaction procedures and analysis cf. Table 5. [b] 0.1 mol of isobutane was passed through the acid solution at a flow rate of 15 ml/min. [c] Based on H_2O_2. [d] Trace of *tert*-butyl sulfate was also observed. [e] Together with ethyl sulfate. [f] Unidentified products were also observed. [g] Tr = traces.

ratio 2:1 at −10 °C (or at room temperature), while isopentane gave methyl alcohol, ethyl alcohol, and acetic acid in the molar ratio 1:1:1 at 40 °C. Under the same reaction conditions, 2,2,3-trimethylbutane gave methyl alcohol and acetic acid in the molar ratio 3:2. The reactions in hydrogen fluoride gave the same products, thus indicating the same reaction pattern as reactions with the other strong acids, despite the fact that hydrogen fluoride cannot form a peracid. This suggests that the oxidation reactions using hydrogen peroxide in strong acids can indeed be due to protonated hydrogen peroxide ($H_3O_2^+$). In HF-SbF_5 or HF-BF_3, similar products are formed as in HF. Further, it should be pointed out that at low temperatures, both magic acid and fluorosulfuric acid, only protonate water (to the hydronium ion) with no evidence of any hydrolysis. Hydrogen peroxide being a thousand times weaker nucleophile than water would, therefore, be even less expected to form peroxyacids (*i.e.* Caro's acid). The effective hydroxylating agent consequently is considered to be the hydroperoxonium ion, $H_3O_2^+$. Direct observation of the latter as a static species (similar to the H_3O^+ ion) in superacidic systems was not possible owing to rapid intramolecular hydrogen exchange or exchange with the solvent system, probably involving diprotonated hydrogen peroxide $H_4O_2^{2+}$.

The product pattern in the reaction of tertiary isoalkanes with hydrogen peroxide in superacid solutions can be summarized as follows:



2.3.2. Straight-Chain Alkanes

Under the same reaction conditions as employed in the case of branched-chain alkanes, straight-chain alkanes such as ethane, propane, butane, and even methane give related oxygenation products[68] (Table 9).

Methane, when reacted with hydrogen peroxide-magic acid above 0 °C, gave mainly methyl alcohol. A similar result is obtained with hydrogen peroxide-FSO_3H at 60 °C. Ethane with hydrogen peroxide-magic acid at −40 °C gave ethyl alcohol.

The reaction of propane with hydrogen peroxide took place more easily than that of methane or ethane and yielded isopropyl alcohol as the initial oxidation product. On raising the temperature, isopropyl alcohol gave acetone, which underwent further oxidation with hydrogen peroxide, giving dimeric acetone peroxide, methyl acetate, methyl alcohol, and acetic acid, as mentioned previously. The related reaction of butane with

Table 9. Products of the reaction of straight chain alkanes with H_2O_2 (molar ratio 1:6) in strong acids.

Acid	Alkane	Reaction Temp. [°C]	Major Products [a]
Magic acid	CH_4	0, 20	CH_3OH
FSO_3H	CH_4	60	CH_3OH
Magic acid-SO_2ClF	C_2H_6	−40	C_2H_5OH
	C_3H_8	−78	$(CH_3)_2CHOH$ (40 %), $(CH_3)_2C{=}O$ (60 %)
	C_3H_8	−40	$(CH_3)_2CHOH$ (10 %), $(CH_3)_2C{=}O$ (40 %), DAP [b] (50 %)
FSO_3H	C_3H_8	−78	$(CH_3)_2CHOH$
	C_3H_8	−60	DAP [b]
	C_3H_8	−40	CH_3OH (20 %), CH_3COOH (20 %), CH_3COOCH_3 (60 %)
H_2SO_4 [c]	C_3H_8	0	$(CH_3)_2CHOH$ (50 %), CH_3COOH (30 %), CH_3OH (20 %)

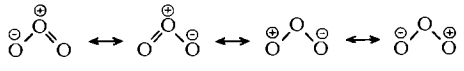
[a] In the case of magic acid systems, conversion is almost 100 % except for methane and ethane reactions. In another systems, no attempt was made to calculate the conversion. [b] Dimeric acetone peroxide. [c] 1 mol of propane was passed through the H_2O_2-acid solution at a flow rate of 15 ml/min.

hydrogen peroxide in magic acid at −78 °C gave *sec*-butyl alcohol. On raising the temperature, *sec*-butyl alcohol was converted into trimethylcarbenium ion. When excess hydrogen peroxide was used in the reaction, the dimethylmethylcarboxonium ion was obtained, formed by the reaction of H_2O_2 with the *tert*-butyl cation and subsequent cleavage-rearrangement of the intermediate *tert*-butyl hydroperoxide *(vide supra)*.

From the products obtained in the reactions, the relative order of reactivity of single bonds in alkanes towards $H_3O_2^+$ was found to be $R_3C{-}H > R_2HC{-}H > RH_2C{-}H > C{-}C$. This order is similar to that observed for electrophilic insertion of protonated ozone, HO_3^+, into the single bonds of alkanes (see Section 2.4).

2.4. Ozonolysis of Alkylcarbenium Ions[78]

In the course of studies on the oxyfunctionalization of hydrocarbons in superacid media, the reaction of ozone towards carbenium ions has also been investigated.

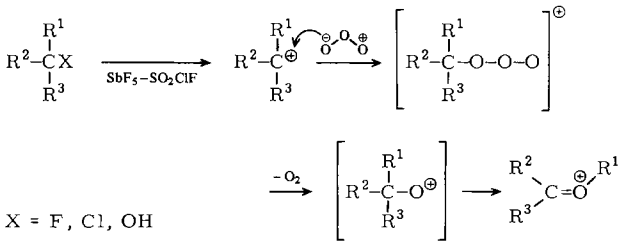


(a) (b) (c) (d)

Since the ozone molecule is shown to be a resonance hybrid of canonical structures (a)—(d)[79], one might expect ozone to react as a 1,3 dipole, an electrophile or a nucleophile. The electrophilic nature of ozone has been recognized in its reactions towards alkenes, alkynes, arenes, amines, sulfides, phosphanes *etc.*[80–84]. Reactions of ozone as a nucleophile, however, are less well documented[85].

As shown in Scheme 23, in the reaction of ozone with carbenium ions[86] the initial attack would be expected to be nucleophilic in nature giving rise to an intermediate trioxide[87], which would then be anticipated to undergo carbon to oxygen alkyl group migration with simultaneous cleavage of a molecule of oxygen, similarly as in the acid catalyzed rearrangement of hydroperoxides to carboxonium ions.

Scheme 23



The products of the reaction of the *tert*-butyl and isopropyl cations with ozone (in oxygen) in magic acid-SO_2ClF solution at −78 °C are listed in Table 10.

Table 10. Products of ozonolysis of alkylcarbenium ions at −78 °C.

Carbenium ion	Conversion [a] of $R^{\oplus}$ [%]	Product Distribution [a]
$(CH_3)_3C^{\oplus}$ [b]	55	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (99 %), $CH_3\overset{\oplus}{C}{=}O$ (trace)
$(CH_3)_2CH^{\oplus}$ [c]	85	$(CH_3)_2C{=}\overset{\oplus}{O}H$ (95 %), $CH_3\overset{\oplus}{C}{=}O$ (5 %), CO_2 [d]

[a] In all experiments, equal amounts of O_3 and $R^{\oplus}$ were used. Conversion of starting material and product distribution were calculated from the ^{1}H-NMR spectrum. [b] $(CH_3)_3CCl$-FSO_3H-SbF_5-SO_2ClF solution. [c] $(CH_3)_2CHCl$-SbF_5-SO_2ClF solution. [d] The ^{13}C-NMR spectrum of this solution indicated the presence of CO_2 ($\delta = 125$).

It should be noted that the isopropyl cation is more reactive towards ozone than the *tert*-butyl cation. This was also confirmed in competitive reactions, in which equimolar amounts of the two cations were ozonolyzed. This also indicates that the reaction can be attributed to the nucleophilic nature of ozone, since the isopropyl cation is more electrophilic than the *tert*-butyl cation.

In the reaction, further oxidation products such as CH_3CO^+ and CO_2 are also formed. These products could not be accounted for by the reaction of ozone with either carbenium ions or the subsequently formed carboxonium ions or their hydrolysis products (ketones, aldehydes and alcohols) in the superacidic media. It must be assumed that oxygen liberated in the rearrangement step is in its highly reactive singlet state and is as such responsible for the further oxidation products.

2.5. Electrophilic Oxygenation of Alkanes with Ozone in Superacids

2.5.1. Branched Alkanes[87]

When a stream of oxygen containing 15 % ozone was passed through a solution of isobutane in FSO_3H-SbF_5-SO_2ClF solution held at −78 °C, the colorless solution immediately turned brown in color. ^{1}H-NMR and ^{13}C-NMR spectra of the resultant solution were consistent with formation of the dimethylmethylcarboxonium ion in 45 % yield together with trace amounts of acetylium ion (CH_3CO^+)[88].

Similar treatment of isopentane, 2,3-dimethylbutane, and 2,2,3-trimethylbutane resulted in formation of related carboxonium ions as the major product (Table 11).

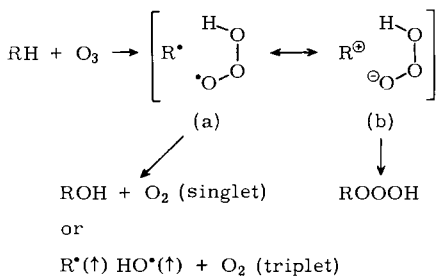
Table 11. Products of the reaction of branched alkanes with ozone in magic acid-SO_2ClF at $-78°C$ [a].

Alkane	Major Products
	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$
	$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$
	$(CH_3)_2C{=}\overset{\oplus}{O}CH(CH_3)_2$ (60 %), $(CH_3)_2C{=}\overset{\oplus}{O}H$ (40 %)
	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (50 %), $(CH_3)_2C{=}\overset{\oplus}{O}H$ (50 %)

[a] In all experiments, a three-to-four mol excess of ozone to alkanes was used. Conversion of alkanes was almost 100 % in all cases. (For equimolar amounts of ozone and alkane, 45 % of isobutane, and 40 % of isopentane were observed.) [b] Product distributions were calculated from the ^{1}H-NMR spectrum. Spectroscopy indicated the presence of CO_2 in most reaction solutions. Major products as shown in the Table represent up to 90—95 % of all products.

It has been reported that the first step in the ozonization of alkanes has some characteristics of a radical reaction and some of an insertion reaction[89]. However, there is still considerable doubt as to the nature of the initial intermediate depicted in Scheme 24[90].

Scheme 24

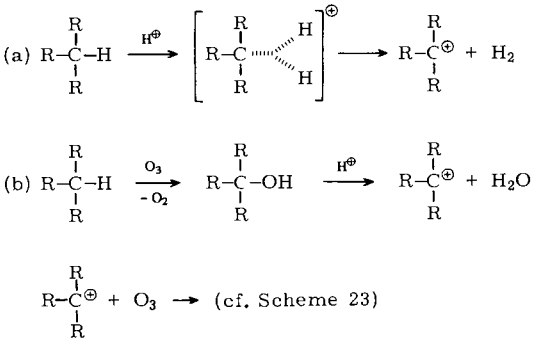


Varkony, *Pass* and *Mazur*[47] proposed formation of an ozone-hydrocarbon complex, followed by electrophilic insertion of oxygen into a C—H bond, whereas *Hellmann* and *Hamilton*[90] favor the species (a) as the major contributing form since this would readily undergo O—O bond cleavage leading to formation of the observed products. Contributions from (b), which would give the trioxide, were considered to be insignificant, since experiments by *Whiting*[91] showed no evidence for a trioxide intermediate in the ozonization of alkane under conditions where the trioxide formed in isopropyl alcohol oxidation is readily detected.

In reactions under superacidic conditions a possible pathway is the formation of an alkylcarbenium ion *via* protolysis of the alkane[75] prior to the ozone quenching of that ion, as shown in Scheme 25 (route (a)). Alkylcarbenium ions may also be generated *via* initial oxidation of the alkane to an alcohol followed by protonation and dehydration (route (b)); there have already been a number of reports of ozone reacting with alkanes to give alcohols and ketones[90-92]. In both cases, intermediary alkylcarbenium ions would then undergo nucleophilic reaction with ozone (see Scheme 23).

The products obtained from isobutane and isoalkanes are in accord with either of the reaction pathways shown in Scheme 25.

Scheme 25



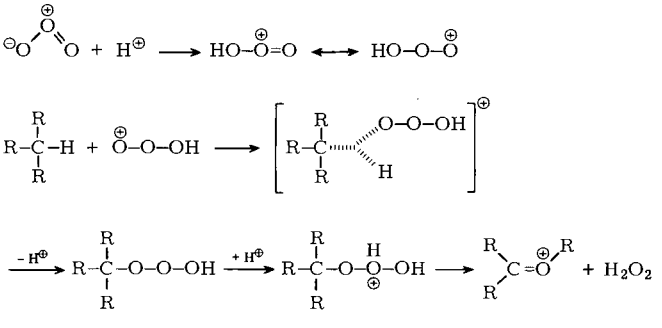
However, it should be noted that the rate of formation of the dimethylmethylcarboxonium ion from isobutane is considerably faster than that of the trimethylcarbenium ion from isobutane in the absence of ozone under the same conditions. Indeed, a solution of isobutane in excess magic acid-SO_2ClF solution showed only trace amounts of the trimethylcarbenium ion after standing for five hours at $-78°C$. Passage of a stream of oxygen gas through the solution—for ten times longer a period than in the ozonization experiments—showed no effect. It was only when ozone was introduced into the system, that rapid reaction took place.

On the other hand, *tert*-butyl alcohol itself in magic acid-SO_2ClF solution gave readily and quantitatively the trimethylcarbenium ion, even at $-78°C$; in the presence of ozone under the same conditions it gave the dimethylmethylcarboxonium ion.

Although isobutane did not give any oxidation products in the absence of magic acid under the same low temperature ozonization conditions, it was not possible to determine whether formation of intermediate oxidation products, such as alcohols, plays any role in the ozonization of alkanes in magic acid. There is no experimental evidence that for reactions proceeding *via* the intermediacy of carbenium ions initial oxidation of the alkanes to alcohols is important. This oxidation, indeed was found to be extremely slow in the acidic media studied.

One may on the other hand also postulate another path for these reactions, namely electrophilic attack by protonated ozone on the alkanes, resulting in oxygen insertion into the involved σ bonds (Scheme 26).

Scheme 26



Since ozone has a strong 1,3-dipole[79,93], or at least strong polarizability, even if a singlet biradical structure is also fea-

sible, it thus is expected to be readily protonated in superacids, in an analogous manner to its alkylation by alkylcarbenium ions. Protonated ozone, O_3H^+, once formed should have a much higher affinity (*i.e.* be a more powerful electrophile) for σ-donor single bonds in alkanes than neutral ozone. It thus would be expected to initiate ozonolysis of alkanes, in a similar manner to nitrolysis by the nitronium ion NO_2^+[77], chlorolysis by the incipient chloronium ion Cl^+[76], or the more generally studied protolysis by superacids[75].

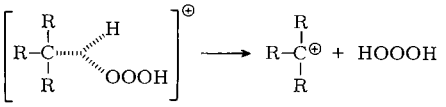
Attempts to directly observe protonated ozone by ^{1}H-NMR spectroscopy, were inconclusive because of hydrogen exchange and the difficulty in differentiating between the chemical shifts of HO_3^+ and H_3O^+.

Alkyl hydrotrioxides have been proposed as intermediates in the decomposition of *tert*-alkyl hydroperoxides with lead tetraacetate[94] and in the ozonization of ethers[95], aldehydes[96], and alcohols[97].

More recently, *Bartlett* and *Lahar*[98] isolated crystalline trioxides, stable below −30°C, by ozonolysis of *tert*-butyl hydroperoxide, of the sodium salt of *tert*-butyl hydroperoxide, and of the sodium salt of cumyl hydroperoxide.

$$RO^\bullet + ROOH \rightarrow ROH + ROO^\bullet$$
$$RO^\bullet + ROO^\bullet \rightleftharpoons ROOOR$$

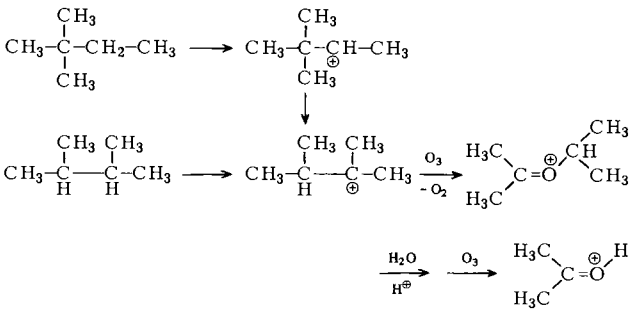
Another possible mode of cleavage of the activated complex of Scheme 26 would give an alkylcarbenium ion and hydrogen trioxide.



Although extremely unstable, hydrogen trioxide was detected; it decomposes into water and oxygen[99].

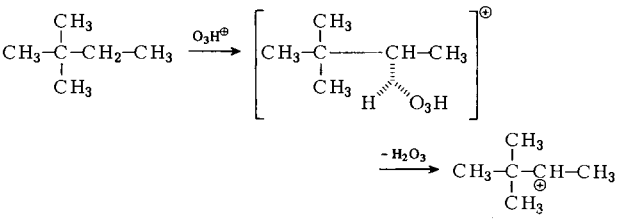
2,2-Dimethylbutane and 2,3-dimethylbutane in magic acid solution gave almost the same distribution of major products upon treatment with ozone at −78°C, namely dimethylisopropylcarboxonium ions and protonated acetone in the ratio 3:2. This clearly demonstrates the intermediacy of alkylcarbenium ions in these reactions (Scheme 27).

Scheme 27



The methyl-*tert*-butylcarbenium ion can be derived from the pentacoordinated carbonium ion by cleavage of hydrogen trioxide.

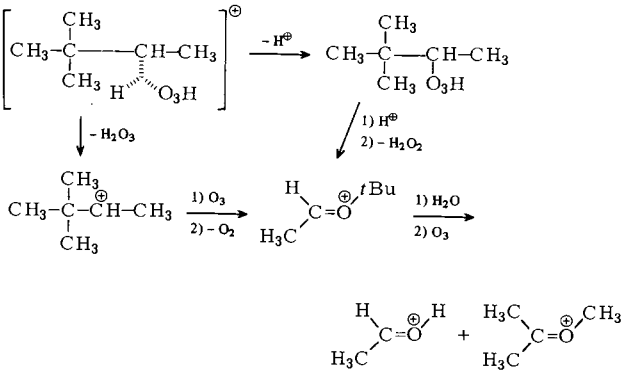
Isopropyl alcohol, the expected hydrolysis product of the dimethylisopropylcarboxonium ion could not be observed in either reaction. Isopropyl alcohol can, however, readily



undergo ionization giving first the isopropyl cation which can then react with ozone and form acetone. Indeed, after completion of the ozonization reaction at −78°C, concomitant formation of acetone and disappearance of the carboxonium ion was observed on increasing the temperature to −20°C. However, the observed amount of isopropyl alcohol was almost negligible. It is thus reasonable to assume that the isopropyl alcohol formed from the carboxonium ion reacts with hydrogen peroxide or trioxide, which in turn are respectively formed as shown in Scheme 26 from protonated ozone and an alkane.

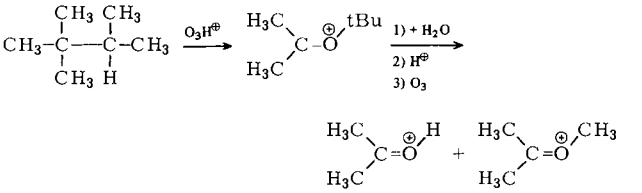
In the reaction of 2,2-dimethylbutane, some acetaldehyde and dimethylmethylcarboxonium ion was also obtained. These can be formed as shown in Scheme 28.

Scheme 28



2,2,3-Trimethylbutane gave protonated acetone and dimethylmethylcarboxonium ions in the ratio 1:1 (Scheme 29).

Scheme 29

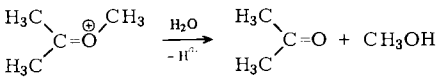


The carboxonium ion intermediate could not be detected under the conditions employed; it is very unstable and decomposes into acetone and dimethylmethoxycarbenium ion.

The observed reactions of alkanes with ozone in superacid media indicate initial electrophilic attack of HO_3^+ at the single σ-bond of alkanes.

In order to provide further evidence in support of the ozonization reaction *via* protonated ozone, the reactions were also studied in the presence of weaker acids such as HF-BF_3, FSO_3H, and H_2SO_4 under conditions in which the acids themselves do not react with any of the alkanes studied to give alkylcarbenium ions. Ozonolysis of alkanes in these acids

yielded products identical to those formed in magic acid (cf. Table 11). Consequently, these results afford further proof that the reactions involve electrophilic oxygenation of the alkanes by HO_3^+. The yield of dimethylmethylcarboxonium ion obtained in the reaction of isobutane with ozone in SO_2ClF solutions of these weaker acids at $-78\,^\circ C$ systems was, however, low (5—10 %). Ozone in the presence of these acids thus seems to be less effectively protonated than in the presence of magic acid. Another aspect of this reaction must also be taken into consideration: the formation of methanol and acetone, which are formed by hydrolysis of the intermediary carboxonium ions.



Since there is little water present in the system at the outset of the reaction, it must be formed as the reaction proceeds. A probable source of water is hydrogen trioxide[99], formed from cleavage of the pentacoordinated carbonium ion in the hydrogen abstraction step.

$$H_2O_3 + H^\oplus \rightarrow H_3O^\oplus + O_2$$

The hydrolysis of carboxonium ions in magic acid solution at $-78\,^\circ C$ is not significant, as water formed is protonated to give H_3O^+, thus deactivating it as a nucleophile. With increasing temperature, however, there is increased hydrolysis, since the carbonium ion deprotonation equilibrium is favored.

2.5.2. Straight Chain Alkanes

Under the same ozonization conditions (magic acid in SO_2ClF at $-78\,^\circ C$), ethane gave protonated acetaldehyde as the major reaction product together with some acetylium ion (Scheme 30, Table 12).

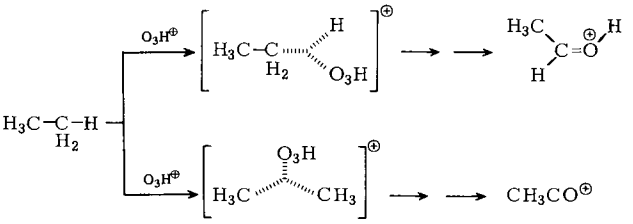
Table 12. Products of the reaction of straight chain alkanes with ozone in magic acid-SO_2ClF [a].

Alkane	Reaction Temp. [°C]	Major Products	
CH_4	−50 [b]	$(CH_3)_2C{=}\overset{\oplus}{O}H$	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$
C_2H_6	−78	$CH_3(H)C{=}\overset{\oplus}{O}H$	
C_3H_8	−78	$(CH_3)_2C{=}\overset{\oplus}{O}H$	
C_4H_{10}	−78	$CH_3(H)C{=}\overset{\oplus}{O}C_2H_5$	$C_2H_5(CH_3)C{=}\overset{\oplus}{O}H$
	20 [b]	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$	
C_5H_{12}	−78	$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$	$(C_2H_5)_2C{=}\overset{\oplus}{O}H$
		$C_3H_7(H)C{=}\overset{\oplus}{O}CH_3$	$C_2H_5(C_3H_7)C{=}\overset{\oplus}{O}H$

[a] Cf. footnotes [a] and [b] in Table 11. (For equimolar amounts of ozone and alkane (propane, butane and pentane), around 30 % conversion of alkane was observed.) [b] A mixture of 4 mol excess ozone and alkane was passed through magic acid-SO_2ClF. For room temperature reactions neat magic acid was used.

Propane gave mainly protonated acetone (90 %) together with some acetylium ion. These products, excluding the acetylium ion, could also be derived from the corresponding alkyl-

Scheme 30



carbenium ions formed by the protolysis of the alkanes, which are attacked nucleophilically by ozone.

However, the product distributions obtained are not in accord with those predicted on the basis of the order of protolytic reactivity of single bonds in alkanes, *i.e.* $R_3C{-}H > C{-}C > R_2HC{-}H > RH_2C{-}H$[75]. Thus, if carbenium ions are first formed, the major product should be protonated formaldehyde (*via* the methyl cation) in the case of ethane, and protonated acetaldehyde in the case of propane (*via* the ethyl cation).

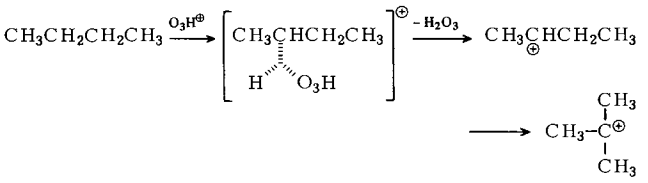
As mentioned above, the reactivity of single bonds of alkanes towards electrophiles generally shows the decreasing order tertiary C—H > C—C > secondary and primary C—H. This order agrees with the experimental data, not only of the protolysis[75], but also of the chlorolysis[76] and the nitrolysis[77] of ethane and propane. However, as pointed out previously[75], additional factors such as, for example, steric hindrance, can influence the relative order of reactivity; therefore, the findings must be limited to the specific system studied. Thus, the relative reactivity of the alkane single bonds towards HO_3^+ (ozonolysis) might be expected to differ from that towards H^+ (protolysis) because of the bulkiness of the protonated ozone. Consequently, preferential ozonolysis would occur at the more available C—H bonds of ethane and secondary C—H bonds in propane to give subsequently protonated acetaldehyde and acetone, respectively.

When treated with ozone in magic acid-SO_2ClF solution at $-78\,^\circ C$, butane gave protonated methyl ethyl ketone and methylethylcarboxonium ions (the former in slight excess), together with lesser amounts of the dimethylmethylcarboxonium ions and acetylium ions.

It should again be noted that the alkylcarbenium ions expected to be formed on protolysis of butane, cannot give methyl ethyl ketone and methylethylcarboxonium ion as the main products after nucleophilic ozonization, because of the general preference in magic acid solution of C—C over C—H bond protolysis. One would expect these main products to be formed by reaction of ozone with the *sec*-butyl cation, which can be formed by protolysis of secondary C—H bonds in butane or by dehydration of *sec*-butyl alcohol, the initial oxidation product of butane. However, attempts to obtain the *sec*-butyl cation from butane or 2-butanol in the absence of ozone under the reaction conditions ($-50\,^\circ C$) resulted only in the formation of the trimethylcarbenium ion; in the latter case protonated *sec*-butyl alcohol was also found. Consequently, even if the initial product of oxidation of butane were 2-butanol, it would subsequently give exclusively the dimethylmethylcarboxonium ion. Indeed, under similar reaction conditions at $-78\,^\circ C$, 2-butanol did not react with ozone, but as the temperature was raised above $-50\,^\circ C$ reaction did occur, yielding the dimethylmethylcarboxonium ion.

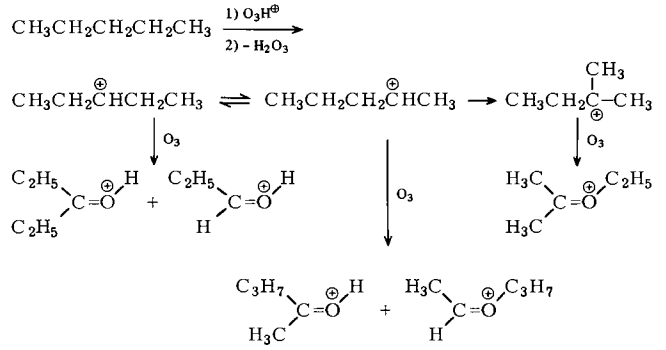
The oxygenation of secondary C—H bonds of butane with HO_3^+, which seems to have precedence over reaction with C—C bonds, can give methyl ethyl ketone and methylethylcarboxonium ion as the major products. However, in sharp contrast to isobutane and other branched alkanes, it should be noted that in order to form the dimethylmethylcarboxonium ion, even though it is a minor product, skeletal rearrangements involving methyl and hydrogen migration must occur in the course of reaction. In fact when the reaction was carried out at room temperature, the major product was the dimethylmethylcarboxonium ion, strongly indicating in this case the formation of an alkylcarbenium ion prior to reaction with ozone.

These data conclusively show that in the oxygenation with HO_3^+, the carbonium ion transition state can cleave losing hydrogen trioxide to give the incipient primary of the secondary butyl cations, followed by rearrangement *via* methyl (hydrogen) migration to the trimethylcarbenium ion.



When treated with ozone in magic acid-SO_2ClF at $-78\,°C$, pentane gave more complex products, with the dimethylethylcarboxonium ion as one of the major products. This indicates that significant skeletal rearrangement of the linear molecule occurs, even at $-78\,°C$ (Scheme 31).

Scheme 31



Brouwer and *Oelderick* have found that the isomerization of the secondary to the tertiary butyl cation proceeds much slower than in the case of higher alkyl cations, in agreement with the results described here.

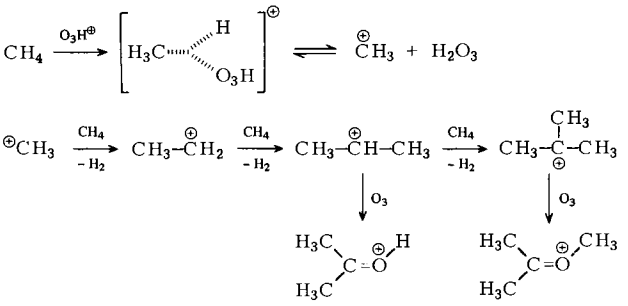
The other major identified product in the reaction was protonated diethyl ketone, which could arise from direct nucleophilic attack by ozone of the diethylcarbenium ion, or by electrophilic insertion by HO_3^+ into the secondary C—H bond in pentane.

Further evidence for initial electrophilic attack by HO_3^+ comes from the reaction of methane with ozone in magic acid.

When an equimolar mixture of methane and ozone was passed through magic acid-SO_2ClF solution at $-50\,°C$ the major reaction product was protonated acetone (see Table 12), whereas reaction in neat magic acid at room temperature afforded preferably the dimethylmethylcarboxonium ion. No formaldehyde could be detected on NMR spectroscopic analysis of the products.

These findings indicate that the reaction is almost exclusively nucleophilic oxygenation by ozone of the alkylcarbenium ions which arise from the oligocondensation of methane (Scheme 32).

Scheme 32



It was previously reported that methane can undergo oligomerization in magic acid solution giving ethane, propane, isobutane, and higher alkanes *via* the corresponding carbocations[101]. However, this reaction generally takes place only above 60 °C. Indeed, when a stream of methane was passed through 20 % magic acid solution in SO_2ClF at a flow rate of 10 ml/min at $-30\,°C$ for 48 hours, only trace amounts of the trimethylcarbenium ion could be detected in the resultant solution. Since significant amounts of oxyfunctionalized products were obtained in the presence of ozone under the same conditions with a reaction time of 6 hours, formation of alkylcarbenium ions from methane under these conditions seems to be a consequence of the electrophilic attack of HO_3^+ at the C—H bonds of methane. Alternatively it could be visualized that the formation of carbenium ions in the absence of ozone is slow, because of the unfavorable equilibrium

$$RH + H^{\oplus} \rightleftharpoons R^{\oplus} + H_2$$

This equilibrium, however, does not seem to be of major significance at low concentrations and atmospheric pressure of H_2.

2.5.3. Behavior of Peroxy Compounds formed from Alkanes and Ozone

Attempts to directly observe protonated ozone by ^{1}H-NMR spectroscopy were inconclusive because of difficulty in differentiating between the chemical shifts of HO_3^+ and H_3O^+. In principle, however, it should be possible to distinguish between the electrophilic insertion by HO_3^+ (Scheme 19) and the nucleophilic reaction with O_3 (Scheme 23 and 25), since in the former case hydrogen peroxide should be formed, while in the latter case oxygen is formed as the cleavage-product of the intermediary trioxide. Analysis of the final reaction solution for hydrogen peroxide proved negative. However, it is known that hydrogen peroxide reacts readily not only with ozone[102], but also with alkylcarbenium ions, and with alkanes in acid solution (as discussed previously). Hydrogen peroxide formed in the reaction of alkanes with ozone in magic acid-SO_2ClF solution therefore would react further by one or more of the above mentioned reactions. In a more detailed study[58]

of the temperature dependence of the reaction of normal alkanes with ozone in FSO_3H-SbF_5-SO_2ClF solution the formation of alcohols was observed. For example, in the oxidation reaction of propane at −78 °C there is almost exclusive formation of (protonated) acetone with 30 % conversion of the alkane. When raising the temperature to −65 °C in the absence of ozone for 2 hours, the formation of isopropyl alcohol was observed. A similar observation was made for ethane at −40 °C and butane at −65 °C, respectively (Table 13).

Table 13. Effect of secondary reactions [a] on the product distribution in the reaction of straight chain alkanes with ozone in magic acid-SO_2ClF.

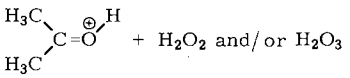
Alkane	Temp. [b] [°C]	Reaction Time [b] [min]	Product Distribution [%] [c]
C_2H_6	−78	0	$CH_3(H)C{=}\overset{\oplus}{O}H$ (≈95 %) [d]
C_2H_6	−78	120	
C_2H_6	−40	60	$CH_3(H)C{=}\overset{\oplus}{O}H$ (90 %), $C_2H_5\overset{\oplus}{O}H_2$ (10 %)
C_3H_8	−78	0	$(CH_3)_2C{=}\overset{\oplus}{O}H$ (≈95 %) [d]
C_3H_8	−78	120	$(CH_3)_2C{=}\overset{\oplus}{O}H$ (≈95 %)
C_3H_8	−65	60	$(CH_3)_2C{=}\overset{\oplus}{O}H$ (85 %), $(CH_3)_2CH{-}\overset{\oplus}{O}H_2$ (15 %)
C_4H_{10}	−78	0	$C_2H_5(CH_3)C{=}\overset{\oplus}{O}H$ (40 %), $CH_3(H)C{=}\overset{\oplus}{O}C_2H_5$ (60 %) [d]
C_4H_{10}	−78	120	$C_2H_5(CH_3)C{=}\overset{\oplus}{O}H$ (40 %), $CH_3(H)C{=}\overset{\oplus}{O}C_2H_5$ (60 %)
C_4H_{10}	−65	60	$C_2H_5(CH_3)C{=}\overset{\oplus}{O}H$ (30 %), $CH_3(H)C{=}\overset{\oplus}{O}C_2H_5$ (50 %), $C_2H_5(CH_3)CH{-}\overset{\oplus}{O}H_2$ (20 %) [e]

[a] Equal amounts of ozone and alkane were used in the presence of a threefold excess of FSO_3H-SbF_5-SO_2ClF at −78 °C. Conversion of propane and normal butane was around 30—40 %. Then, the reaction solution was allowed to stand at the given temperature [b]. For ethane, the mixture of alkane and ozone (1 : 1 molar ratio) was passed through the acid solution at −78 °C. Then the ethane was passed through into the resultant solution without O_3/O_2 gas at the given temperature [b]. [b] The temperature and time of secondary reactions. [c] Product assignments were made as described in Table 5. [d] $CH_3\overset{\oplus}{C}{=}O$ and CO_2 were found as minor products. [e] $(CH_3)_2C{=}\overset{\oplus}{O}{-}CH_3$ was found as minor product.

The results can be explained as in Scheme 33.

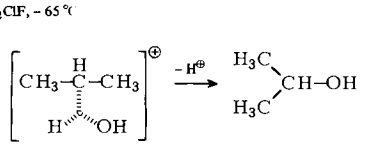
Scheme 33

$$CH_3CH_2CH_3 \xrightarrow[FSO_3H-SbF_5-SO_2ClF,\ -78\,^\circ C]{O_3H^\oplus \text{ and } O_3}$$



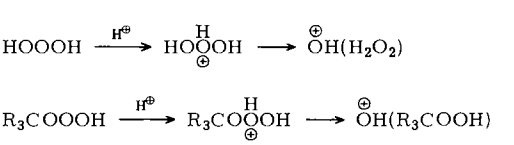
$$+\ H_2O_2 \text{ and/or } H_2O_3$$

$$CH_3CH_2CH_3 \xrightarrow[FSO_3H-SbF_5-SO_2ClF,\ -65\,^\circ C]{H_2O_2 \text{ or } H_2O_3}$$



On the other hand, tertiary isoalkanes did not give any alcohols under these conditions. It is considered that a tertiary alcohol, once formed, would readily undergo ionization in the superacid to give the corresponding alkylcarbenium ion, which would then undergo further reaction with ozone or with excess hydrogen peroxide. Indeed, *tert*-butyl alcohol in FSO_3H-SbF_5-SO_2ClF gives readily and quantitatively the trimethylcarbenium ion, even at −78 °C, and dimethylmethylcarboxonium ion when ozone or hydrogen peroxide is present.

Upon electrophilic insertion by protonated ozone into the C—H bonds of alkanes the formation of not only hydrogen peroxide but other peroxy compounds, such as hydrogen trioxide and alkyl hydrotrioxides, is expected. These peroxy compounds also can be considered to have hydroxylating ability for alkanes.



2.5.4. Neoalkanes

When a stream of oxygen containing ≈5 % ozone was passed through a solution of neopentane in FSO_3H-SbF_5-SO_2ClF at −78 °C the ^{1}H-NMR and ^{13}C-NMR spectra of the resultant solution showed the formation of the dimethylethylcarboxonium ion as the major product, together with dimethylmethylcarboxonium ion and (protonated) neopentyl alcohol. The conversion of the alkane was found to be almost 100 %. The results obtained under various reaction conditions are summarized together with those for 2,2,3,3-tetramethylbutane in Table 14.

The possible reaction pathways for the reaction of neopentane with ozone in FSO_3H-SbF_5-SO_2ClF at −78 °C are shown in Scheme 34.

The reaction course under conditions where dimethylethylcarboxonium ion is formed almost exclusively, can be best explained by the alternative reaction path (a) involving C—H bond ozonolysis, H_2O_3 elimination from the carbonium ion transition state, formation of the neopentyl cation being followed by immediate rearrangement to the *tert*-pentyl cation and its quenching by ozone.

It should be emphasized that the protolysis of neopentane in FSO_3H-SbF_5-SO_2ClF solution at −78 °C is very slow and can be neglected. In fact, after 5 hours at −40 °C, no formation of any kind of alkylcarbenium ion can be detected in the solution. It was only when ozone was introduced into the system that rapid reaction took place under these conditions. However, when the reaction was carried out at temperatures above 0 °C, the formation of dimethylmethylcarboxonium ion was predominant. Under these conditions, as shown in Scheme 35, alkylcarbenium ion formation *via* σ-bond protolysis of neopentane is preferential. Intermediate alkylcarbenium ions would then undergo nucleophilic reaction with ozone to give the corresponding carboxonium ions.

In FSO_3H-SbF_5-SO_2ClF solution at elevated temperatures, neopentane is known to undergo protolytic C—C bond cleavage [path (b)] giving *tert*-butyl cation[75], which subsequently can give the dimethylmethylcarboxonium ion by quenching with ozone and rearrangement[78].

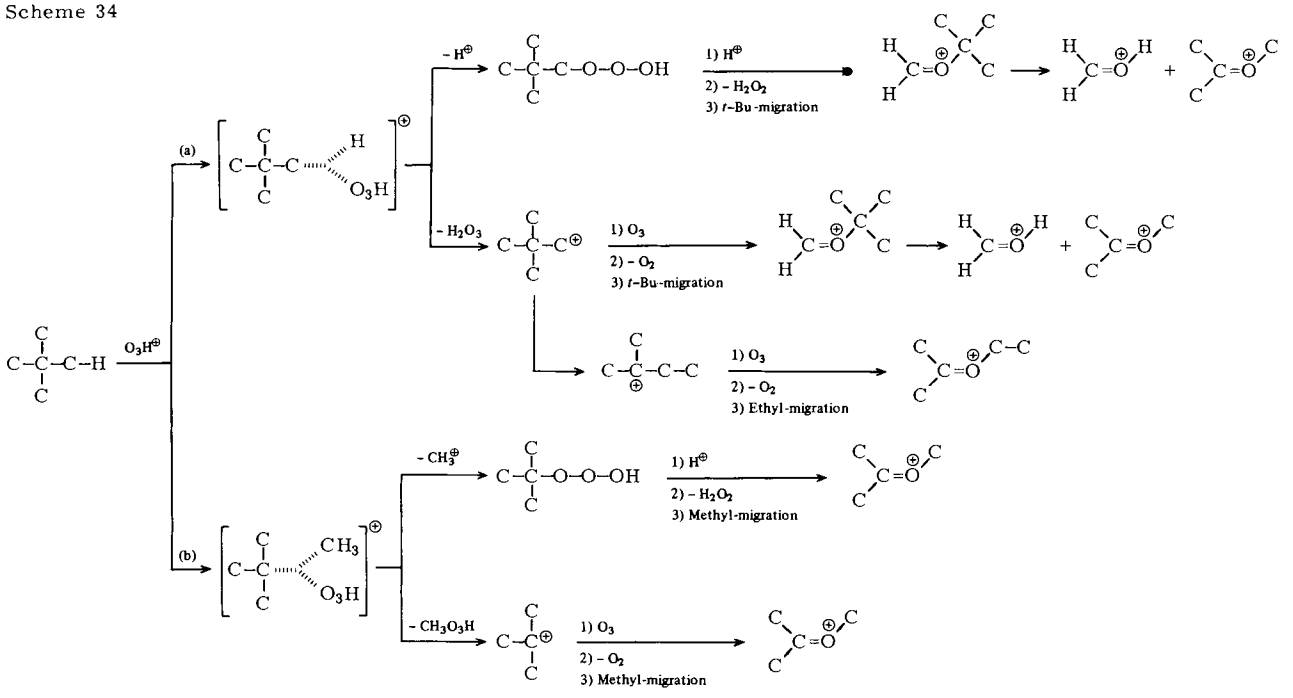
Similar results were also obtained when the reaction was carried out in HF-SbF_5-SO_2ClF or SbF_5-SO_2ClF solution, even at temperatures as low as −78 °C. In these systems,

Table 14. Products of the reaction of neoalkanes with ozone in superacids [a].

Alkane	Acid	Reaction Temp. [°C]	Major Products
	FSO_3H-SbF_5-SO_2ClF	−78	$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$ (95 %), $(CH_3)_3C{-}CH_2\overset{\oplus}{O}H_2$ (5 %)
	FSO_3H-SbF_5-SO_2ClF	−20	$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$ (90 %), $(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (10 %)
	FSO_3H-SbF_5	0	$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$ (15 %), $(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (85 %)
	FSO_3H-SbF_5	+20	$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$ (5 %), $(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (95 %)
	HF-SbF_5-SO_2ClF	−78	$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$ (25 %), $(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (75 %)
	HF-SbF_5-SO_2ClF	−20	$(CH_3)_2C{=}\overset{\oplus}{O}C_2H_5$ (10 %), $(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (90 %)
	FSO_3H-SbF_5-SO_2ClF	−78	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (35 %), $(CH_3)_2C{=}\overset{\oplus}{O}H$ (35 %), $(CH_3)_3C{-}(CH_3)_2C{-}CH_2\overset{\oplus}{O}H_2$ (30 %)
	FSO_3H-SbF_5-SO_2ClF	−50	$(CH_3)_2C{=}\overset{\oplus}{O}CH_3$ (70 %), $(CH_3)_2C{=}\overset{\oplus}{O}H$ (30 %)

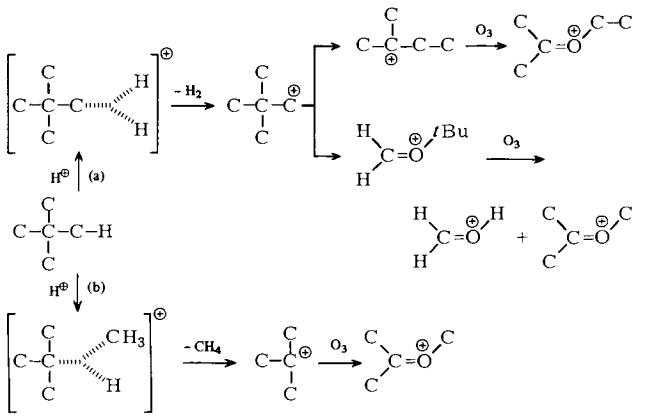
[a] See footnotes [a] and [b] in Table 11.

Scheme 34



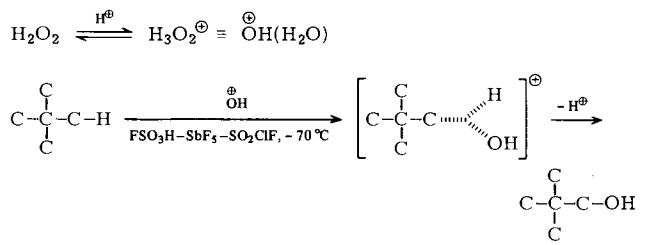
neopentane can undergo protolysis *via* path (a) or path (b) (Scheme 35). In HF-SbF_5-SO_2ClF solution, neopentane readily undergoes protolytic C—C bond cleavage to give *tert*-butyl cation (and methane) [path (b)], while in the presence of ozone under the same conditions the dimethylmethylcarboxonium ion is formed as major product. On the other hand, in SbF_5-SO_2ClF solution, which can be considered always to contain sufficient protic acid impurity to act as an extremely strong superacid, protolytic C—H bond cleavage [path (a)] of neopentane is preferential giving *tert*-pentyl cation and thus in the presence of ozone the dimethylethylcarboxonium ion as the major product. The differing behavior of neopentane depending on the kind of superacid media used reflects the differing nature, such as steric requirements due to differing solvation of the proton, of each system in effecting the reactions of C—C or C—H bonds in neopentane.

Scheme 35



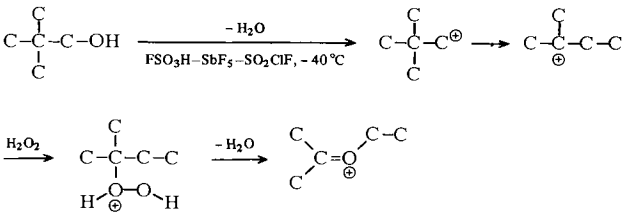
The significant difference between the reaction of neopentane with ozone in FSO_3H-SbF_5-SO_2ClF and in HF-SbF_5-SO_2ClF or SbF_5-SO_2ClF, respectively, is the formation of neopentyl alcohol in the first system. In the case of the reaction of alkylcarbenium ions with ozone (Scheme 28), there is no reason for alcohol formation. On the other hand, under conditions where electrophilic attack of protonated ozone on the σ-bonds of alkanes is preferential, the subsequent formation of hydrogen peroxide or trioxide in the course of the reaction leads to the formation of reactive hydroxylating agents in the superacidic media. Indeed, when neopentane was treated with hydrogen peroxide in FSO_3H-SbF_5-SO_2ClF solution at $-70\,^{\circ}C$, the formation of neopentyl alcohol was observed (Scheme 36).

Scheme 36



Since no other products apart from neopentyl alcohol were observed under the reaction conditions, the attack of protonated hydrogen peroxide on neopentane is exclusively at the C—H bonds. On raising the temperature to $-60\,^{\circ}C$, the rate of formation of the alcohol is remarkably increased. At $-40\,^{\circ}C$, however, formation of *tert*-pentyl cation was observed and when excess hydrogen peroxide was used in the reaction dimethylethylcarboxonium ion was obtained (Scheme 37).

Scheme 37

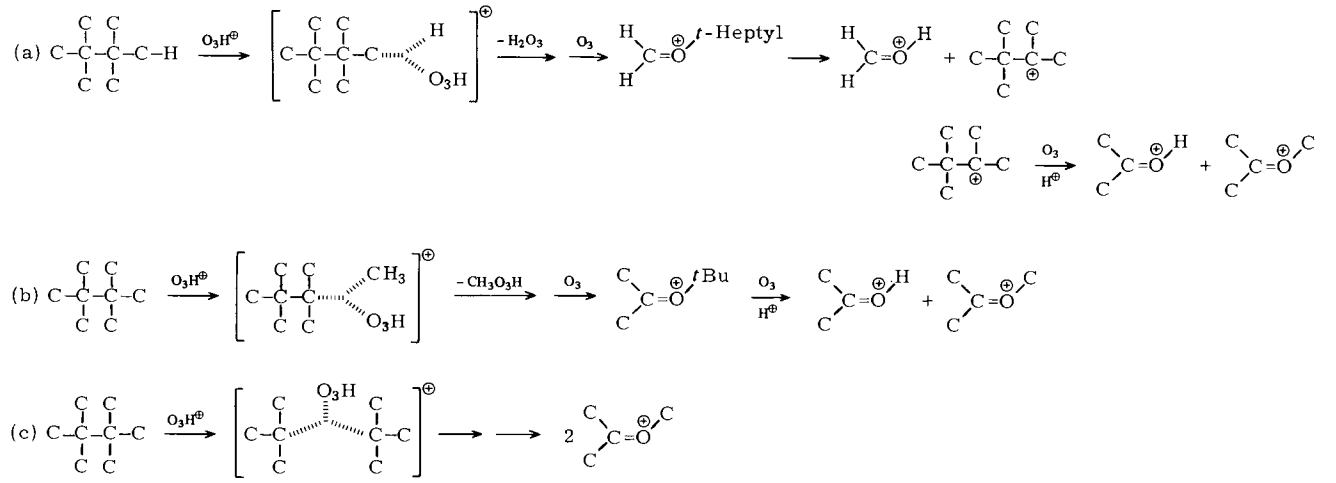


2,2,3,3-Tetramethylbutane, when treated with ozone in FSO_3H-SbF_5-SO_2ClF solution at $-78\,^{\circ}C$ gave dimethylmethylcarboxonium ion and (protonated) acetone together with 2,2,3,3-tetramethylbutyl alcohol as major products. The dimethylmethylcarboxonium ion and acetone were formed in the molar ratio 1:1. Formaldehyde, methyl ethyl ketone, acetylium ion and carbon dioxide were also found in small amounts. These findings once again indicate that the reaction takes place by initial electrophilic σ-bond insertion by protonated ozone into the alkane, as shown in Scheme 38.

Although in principle, the reaction can take place by attack of protonated ozone at either the C—H, C^1—C^2 or C^2—C^3 bond (paths (a), (b) or (c), respectively, in Scheme 38), the reactivity of the C—H bonds is considered to be much higher than that of the sterically highly hindered C^1—C^2 or C^2—C^3 bonds. Indeed, the product distribution obtained shows that there is little C^2—C^3 bond cleavage [path (c)]. Although cleavage of the C^1—C^2 or C—H bonds would also be in accordance with the experimental results (product ratio dimethylmethylcarboxonium ion : acetone = 1 : 1), the results of the reaction of ethane giving almost exclusively acetaldehyde under the same reaction conditions (see Scheme 30) suggest that attack by protonated ozone preferentially takes place at the C—H bonds.

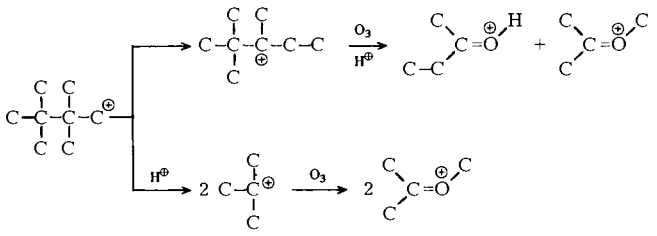
As shown in Scheme 38 (path (a)), elimination of hydrogen trioxide from the pentacoordinated carbonium ion can give the neooctyl cation, which then rearranges to the more stable

Scheme 38



cation tBu(Me)EtC$^+$ or cleave to the *tert*-butyl cation, as shown in Scheme 39. However, no methyl ethyl ketone was formed, and the product distribution shown in Table 14 would suggest that rearrangement or cleavage of the neooctyl cation is only a minor reaction path.

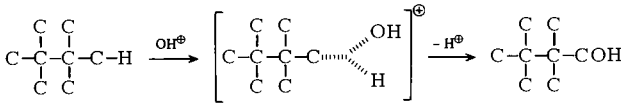
Scheme 39



The *O-tert*-heptylcarboxonium ion has not been observed as long-lived species in solution. It seems to readily decompose, giving formaldehyde and the dimethyl-*tert*-butylcarbenium ion, which then readily reacts with ozone giving the dimethyl-*tert*-butylcarboxonium ion, which in turn immediately cleaves to (protonated) acetone and the dimethylmethylcarboxonium ion. Indeed, the reaction of triptane (2,2,3-trimethylbutane) under the same reaction conditions showed exclusively the formation of dimethylmethylcarboxonium ion and acetone in the ratio 1:1 (see Scheme 29).

2,2,3,3-Tetramethylbutane gave the corresponding alcohol (2,2,3,3-tetramethylbutyl alcohol) in higher yield (30%) than did neopentane (5%) under the same conditions (Scheme 40).

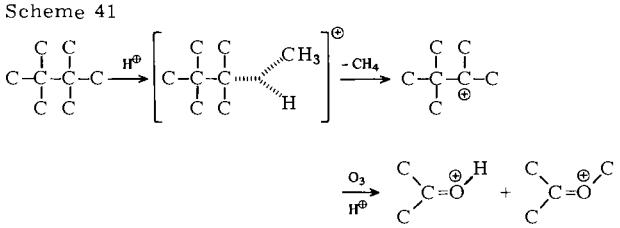
Scheme 40



The differing yields of the corresponding alcohols from neoalkanes seems to reflect the differing reactivity of hydroxylating agent towards the σ-bonds involved. Similar observations were made in the reaction of hydrogen peroxide in the presence of FSO_3H-SbF_5-SO_2ClF. The lowest temperature for formation of the corresponding alcohols is, in the case of methane, ethane, neopentane and 2,2,3,3-tetramethylbutane, about −20, −40, −70 and −75 °C, respectively. The differing reactivity of the C—H bonds in these alkanes is interesting, but the reasons are not yet fully understood.

In HF-SbF_5-SO_2ClF solution, the reaction of 2,2,3,3-tetramethylbutane with ozone gave dimethylmethylcarboxonium ion and protonated acetone in a molar ratio of about 1:1, but no alcoholic products. This clearly demonstrates protolysis of the alkane prior to ozonolysis, as shown in Scheme 41.

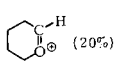
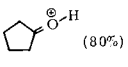
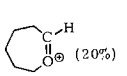
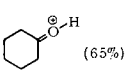
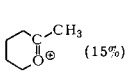
Scheme 41



2.5.5. Cycloalkanes

When cyclopentane was allowed to react with ozone in the presence of FSO_3H-SbF_5-SO_2ClF at −78 °C, the NMR spectra of the resultant solution were consistent with formation

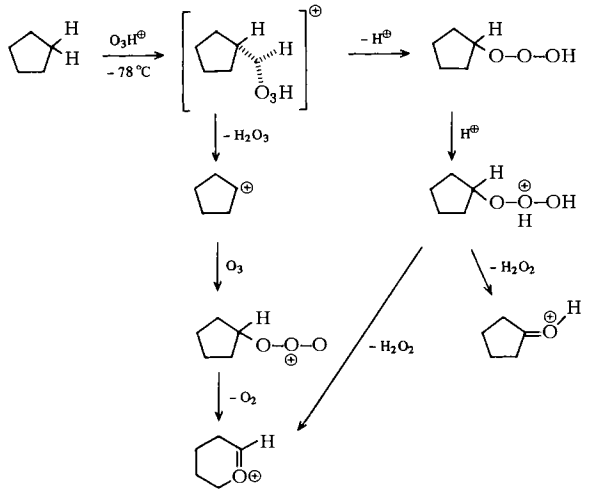
Table 15. Products of the reaction of cycloalkanes in magic acid-SO_2ClF [a].

Alkane	Reaction Temp. [°C]	Oxidizing Agent	Major Products
	-78	O_3	 (20%)  (80%)
	-78	O_3	 (20%)  (65%)  (15%)
	-78	O_3	
	-78	O_3	
	-60	H_2O_2	
	-60	H_2O_2	
	-78	O_3 or H_2O_2	

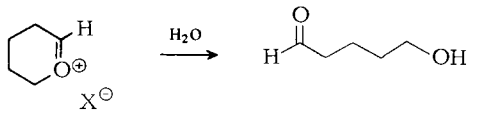
[a] 10 mmol of alkane in threefold excess of magic acid-SO_2ClF solution were treated with 30 mmol of ozone or 5—10 mmol of H_2O_2. See also footnotes [a] and [b] in Table 11.

of protonated cyclopentanone and cyclic carboxonium ions (Scheme 42; cf. Table 15).

Scheme 42



The cyclic carboxonium ion that is formed gives 5-hydroxypentanal on hydrolysis.



The reaction of cycloalkanes with ozone or hydrogen peroxide in the presence of superacids is presently being investigated[67].

2.6. Electrophilic Oxygenation of Functionalized Compounds. Preparation of Bifunctional Derivatives[103]

Despite the high reactivity of protonated ozone with alkanes in superacids, methyl alcohol, acetone or acetaldehyde were not found to be further oxidized by ozone in magic acid-SO_2ClF solution under the reaction conditions employed. In the superacidic system, they are present as completely protonated species, *i.e.* as $CH_3\overset{+}{O}H_2$, $(CH_3)_2C{=}\overset{+}{O}H$ and $CH_3(H)C{=}\overset{+}{O}H$; thus protonated ozone will not readily react with σ-bonds located in the proximity of the carboxonium center in the protonated substrates. On the other hand, σ-bonds which are located sufficiently far away from the charged carboxonium center may be attached and undergo reaction.

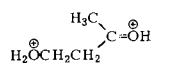
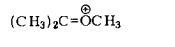
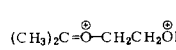
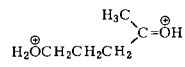
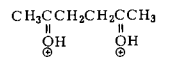
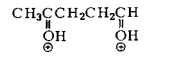
In order to clarify the behavior of oxygenated products in ozone-superacid systems, the reaction of aliphatic alcohols, ketones and aldehydes with ozone in magic acid-SO_2ClF or FSO_3H solution has been investigated.

2.6.1. Alcohols

Alcohols with short alkyl chains, such as methyl, ethyl and propyl alcohol do not react with ozone under superacidic conditions. However, butyl and higher homologous primary alcohols react readily, giving hydroxyketones as products. The products obtained are listed in Table 16.

The data of Table 16 show that tertiary or secondary C—H bonds of primary alcohols located γ- or farther away from the oxonium center undergo insertion reactions with protonated ozone, giving oxidation products in good yield. In general, straight chain primary alcohols give hydroxyketones (in their protonated form), whereas branched chain primary alcohols give dimethyl-ω-oxonioalkylcarboxonium ions. The latter, upon hydrolysis, give acetone and the corresponding glycol.

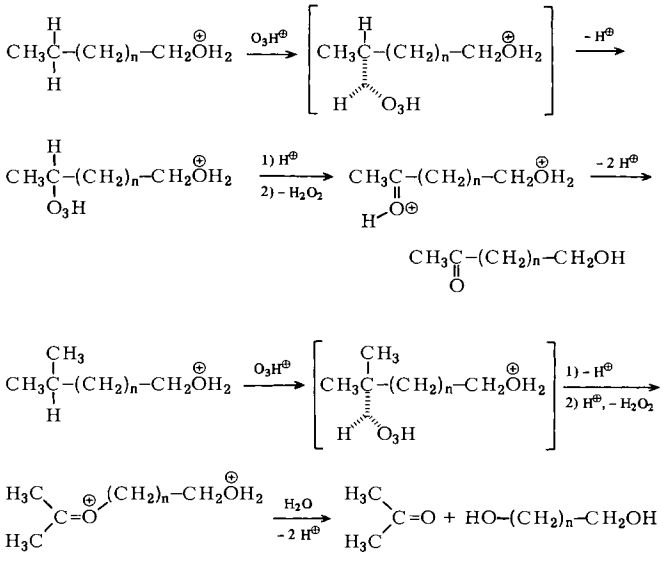
Table 16. Products of the reaction of aliphatic alcohols, ketones and aldehydes with ozone in magic acid [a].

Substrate	Reaction Temp. [°C]	Conversion [b] [%]	Product
$CH_3CH_2CH_2CH_2OH$	-40	30	
$CH_3CH_2\underset{\underset{OH}{|}}{C}HCH_3$	-40	100	
$CH_3\underset{\underset{CH_3}{|}}{C}HCH_2CH_2OH$	-40	60	
$CH_3CH_2CH_2CH_2CH_2OH$	-78	100	
$CH_3CH_2CH_2\underset{\underset{O}{\|}}{C}-CH_3$	-40	[c]	
$CH_3CH_2CH_2CH_2\underset{\underset{O}{\|}}{C}CH_3$	-78	100	
$CH_3CH_2CH_2CH_2\underset{\underset{O}{\|}}{C}H$	-78	80	

[a] See footnotes [a] and [b] in Table 11. [b] Based on substrate. [c] No reaction.

As discussed previously, the relative order of reactivity of σ-bonds in alkanes with protonated ozone is generally $R_3C{-}H > R_2(H)C{-}H, R(H_2)C{-}H > C{-}C$. A similar order of reactivity was found in the reactions of protonated alcohols and carbonyl compounds. 3-Methyl-1-butyl alcohol (with a tertiary C—H bond at the γ position) undergoes reaction with protonated ozone more readily than butyl alcohol (with a secondary C—H bond at the γ position) giving oxidation-rearrangement products as shown in Scheme 43.

Scheme 43



These results are in sharp contrast to those observed in the absence of magic acid. In trichlorofluoromethane solution,

ozonization of alcohols was reported to give exclusively products of α-oxidation, *i.e.* carboxylic acids and ketones[104]. It is thus reasonable to assume that reactions in superacids proceed *via* electrophilic oxygenation of the involved C—H bonds of the alcohols with protonated ozone, analogously to the previously discussed alkanes, as shown in Scheme 43. The superacid fully protonates the hydroxymethyl groups and thus protects them from oxidation.

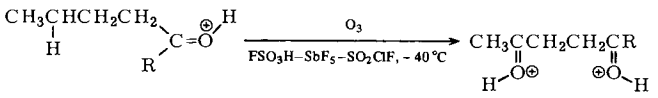
Similar reactions also take place in FSO_3H at −40 °C in the case of aliphatic alcohols in which *n* is larger than 4. However, the yield of bifunctional oxygenated products is lower than that obtained in magic acid-SO_2ClF solution. In the weaker FSO_3H acid, ozone is less completely protonated and is thus a weaker electrophilic reagent than it is in magic acid solution.

2-Propyl and 2-butyl alcohol do not react with ozone in magic acid-SO_2ClF at −78 °C, but at −40 °C they give protonated acetone and dimethylmethylcarboxonium ions, respectively. This indicates that in these systems protolytic ionization of the alcohols takes place at −40 °C, giving rise to the corresponding alkylcarbenium ions, which then readily react with ozone, yielding the oxygenation products described previously.

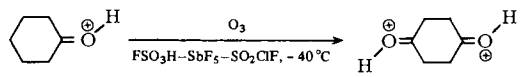
2.6.2. Ketones and Aldehydes

The results of the reactions of aliphatic ketones and aldehydes with ozone in superacids are summarized in Table 16.

In contrast to the behavior of the previously discussed aliphatic alcohols, secondary C—H bonds of aliphatic ketones and aldehydes, such as 2-pentanone, butyraldehyde or cyclopentanone, located γ to the carbonyl oxygen do not react with protonated ozone in the presence of magic acid-SO_2ClF solution at −40 °C. The strong electron-withdrawing effect of the protonated carbonyl group is sufficient to inhibit reaction at these C—H bonds. Higher homologous ketones and aldehydes, however, do react, giving oxygenated products arising from oxygen insertion into farther located σ-bonds.



R = H, CH_3, C_2H_5



In the case of cyclohexanone, the yield of 1,4-cyclohexanedione is low, even at a reaction temperature of −40 °C. However, the reaction of cycloheptanone, having two methylene groups γ to the carbonyl carbon, produces 1,4-cycloheptanedione in 60% yield at −78 °C.

In previously studied ozonolysis reactions of aldehydes with neutral ozone, *White* and *Bailey*[105] and *Erickson et al.*[106] suggested that the attack by ozone is a concerted 1,3-dipolar insertion, having electrophilic character. There was, however, no other attack observed than on the carbonyl carbon. Reactions of ketones with neutral ozone also yielded only products due to attack on the carbonyl carbon[55].

In contrast, using superacidic conditions the reaction with oxygen containing 5% ozone gave no products arising from carbonyl-carbon oxidation. Hence, these reactions can be again best described as involving electrophilic oxygenation of C—H σ-bonds by protonated ozone.

In summary the oxygenation of alkanes in highly acidic (superacidic) media shows promise of developing into a field of substantial interest, allowing the preparation of a wide variety of oxyfunctionalized products in selective, frequently highly productive reactions.

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Use of a Photoelectron Spectrometer in Gas Phase Analysis: Cyanogen and Hydrogen Cyanide[1]

By *Hans Bock*, *Bahman Solouki*, and *Jörg Wittmann*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 75th birthday

Photoelectron spectra permit observation of all Koopmans radical cation states of a molecule, and, therefore, patterns of ionization bands recorded represent a "molecular fingerprint". If the PE spectra of various molecules do not overlap completely, and provided that separate characteristic bands are recognizable, the course of a gas phase reaction can be traced visually: the PE fingerprints of the reactants give way to those of the products, depending on the reactants[2a, b], temperature[2c–e], and pressure[2a]. Moreover, comparison of the intensities of the reactant and product bands—if proportional to concentration—affords information about conversion rates and about detection limits.

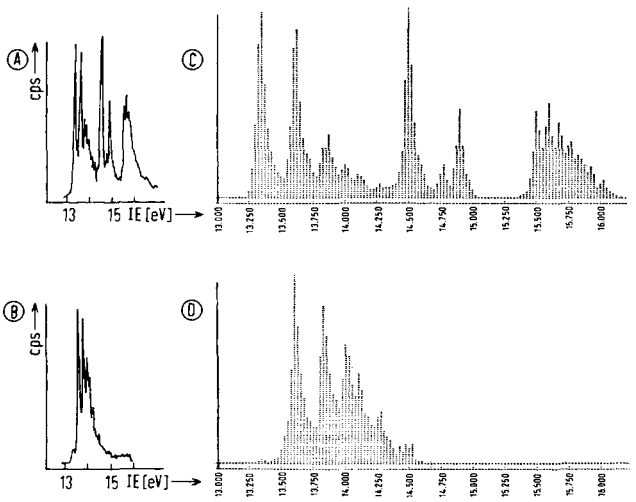


Fig. 1. PE spectra (12—17 eV) of NCCN/HCN mixtures in the partial pressure ratios 75:25 (A) and 2:98 (B), and their computer simulation [3] (C) and (D).

The development and application of a gas phase analytical technique based on PE spectroscopy will be illustrated for the poisonous pseudohalogen derivatives cyanogen and hydrogen cyanide. These gases are mixed in a 1-liter round-bottom flask (fitted with a manometer and attached to the PE spectrometer) in various pressure ratios $P_{NCCN} : P_{HCN}$ and the spectra of the series of mixtures are recorded (Fig. 1: (A) and (B)).

Assuming a linear dependence between PE band intensity and partial pressure, the spectra can be computer-simulated for any mixing ratio (Fig. 1: (C) + (D)). It is advantageous to use the relative intensities of the needle-like peaks at 13.3 eV (NCCN) and 13.6 eV (HCN + NCCN) for the analysis. Obviously, only about 25 parts of HCN in 75 parts of NCCN, but still 2 parts of NCCN in 98 parts of HCN can be detected (Fig. 1).

The PES analysis method, which can be set up within 1—2 days, permits rapid elucidation of gas phase reactions. For instance, on heating of acetonitrile and cyanogen in a quartz flow tube[2b, e], an increase in the peak at 13.6 eV above 1300 K indicates the formation of HCN (Fig. 2 (A): ⇓). If the H_3CCN partial pressure is increased tenfold at the same temperature, then the NCCN signals disappear completely (Fig. 2 (B): ↓). No other PE bands appear; a layer of graphite is deposited outside the furnace zone.

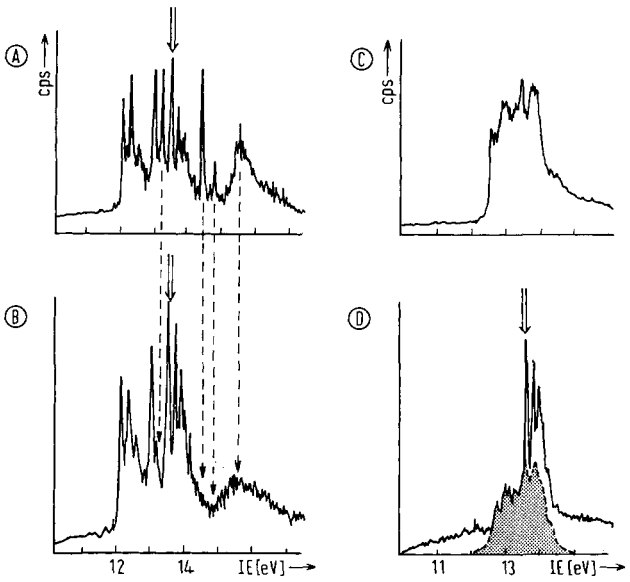
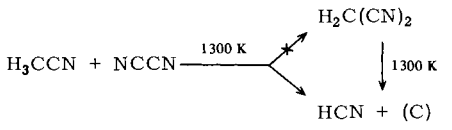


Fig. 2. PE spectra of H_3CCN/NCCN mixtures heated to 1300 K, $P_{H_3CCN} : P_{NCCN} = 1:1$ (A) and 10:1 (B), and of malononitrile at 300 K (C) and 1300 K (D).

Thus the thermal reaction of acetonitrile and cyanogen at 1300 K does not lead to malononitrile but to hydrogen cyanide and carbon:



Pyrolysis of malononitrile at 1300 K confirms that the compound decomposes at this temperature to hydrogen cyanide with deposition of graphite (Fig. 2: (C) + (D)).

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NCCN, 460-19-5; HCN, 74-90-8; H_3CCN, 75-05-8

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[3] A Fortran IV program adapted to PDP 11/40 is available from the authors on request.

Copper-Catalyzed Cyanation of Benzene in the Gas Phase[1, 2]

By *Hans Bock, Bahman Solouki, Jörg Wittmann*, and *Hans-Jürgen Arpe*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 75th birthday

The early tempestuous years of photoelectron spectroscopy—development of the method, commercial production of high-resolution spectrometers, measurement of the ionization patterns of thousands of molecules—have now been superseded by a time of reflection about practical applications[3]. Based on the experience gathered, it is now feasible, for example, to optimize gas phase reactions in a flow tube, including those which are heterogeneously catalyzed, with the aid of continuously recorded PE spectra (Fig. 1).

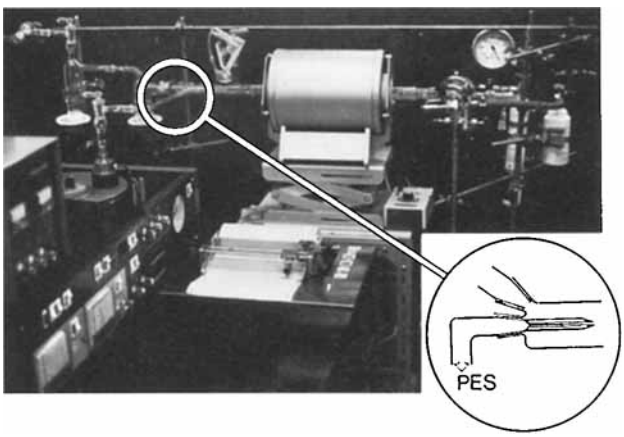
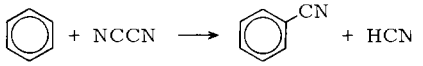


Fig. 1. Apparatus for the study of gas phase reactions on a preparative scale with variation of pressure and temperature [right to left: steel gas containers (warmed if necessary), mixing vessel, furnace with temperature control, bleeding valve to PE spectrometer, cold traps, oil pump].

In the standard apparatus (Fig. 1) the capillary Pitot tube of variable length permits up to 1000-fold reduction of the pressure of the hot gases leaving the reaction tube, at temperatures up to 1500 K, to the PE measuring pressure of about 13 Pa. This apparatus has been used, for instance, to examine the thermal reaction of benzene with cyanogen, employing the PES analysis technique developed for NCCN/HCN mixtures[1]. PES analysis in 50-K steps shows that the reaction[4]



starts at about 1300 K (Fig. 2).

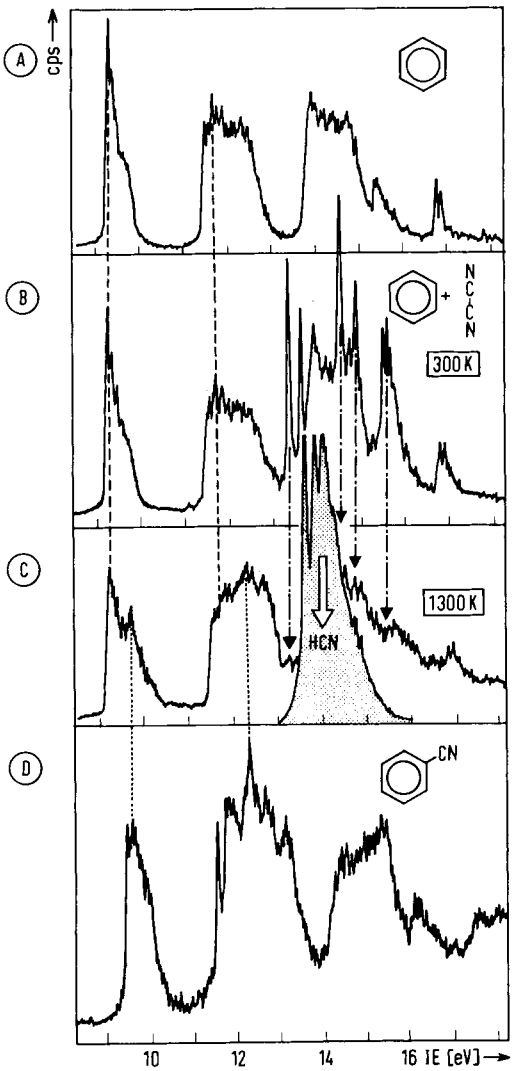


Fig. 2. PE spectrum of benzene (Ⓐ), its mixture with cyanogen at 300 and 1300 K (Ⓑ+Ⓒ), and of benzonitrile (Ⓓ) (assignment: ⇓ HCN, –·–·– NCCN, – – – C_6H_6, ····· C_6H_5CN).

The PE spectra (Fig. 2) clearly show that the bands of NCCN in the benzene/cyanogen mixture at 1300 K are replaced by those of HCN; simultaneously, benzonitrile can be detected.

Various copper catalysts were introduced in screening tests with the aim of reducing the high reaction temperature: a drop of 700 degrees to 600 K has been achieved with Cu/Al_2O_3. Moreover, one observes that the catalyst becomes inactive on raising the temperature to 700 K, only to regain its activity at 800 K—presumably owing to the temporary occupation of the active centers by products and/or undesired side products.

Cyanation of benzene on a preparative scale under conditions optimized by PES (standard apparatus (Fig. 1), Cu/Al_2O_3, 10 torr, 850 K) affords *ca.* 40 wt-% of benzonitrile in a single passage.

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Benzene, 71-43-2; cyanogen, 460-19-5; benzonitrile, 100-47-0

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Diastereoselective Radical Recombination and Variation in Thermal Stability of Diastereomeric Hydrocarbons[**]

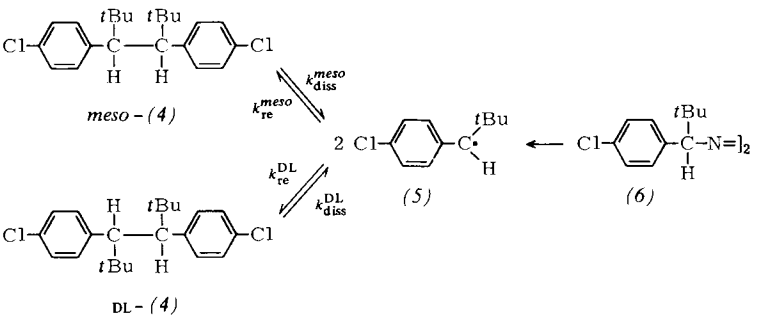
By *Karl-Heinz Eichin, Kevin J. McCullough, Hans-Dieter Beckhaus*, and *Christoph Rüchardt*[*]

Dedicated to Professor Heinrich Hellmann on the occasion of his 65th birthday

The rate of dimerization of simple alkyl radicals in solution is determined by their rate of diffusion[1]; 1-phenylethyl and 2-phenyl-3-methylbutyl each give two diastereomeric dimers in the ratio 1:1[1a,2]. Bulky alkyl radicals such as di-*tert*-butylmethyl or triisopropylmethyl, on the other hand, are persistent[3] and do not dimerize. The dimerization of medium-sized radicals therefore ought to proceed *via* an activation threshold. An indication of this was provided by kinetic investigation of the thermolysis of highly-strained alkanes *(1)*[4], from which it could be concluded that 40% of the strain enthalpy of *(1)* is retained in the transition state *(2)* of homolytic decomposition.

$$R^1R^2R^3C{-}CR^1R^2R^3 \xrightarrow{\Delta} [R^1R^2R^3C\cdots CR^1R^2R^3]^{\ddagger} \longrightarrow 2\ R^1R^2R^3C^{\bullet}$$
(1) *(2)* *(3)*

Hence, the dimerization of *(3)* to *(1)* should also have to overcome a corresponding activation barrier; the distribution of the diastereomeric dimers *(1)* is then no longer random. their dimers *meso*- and DL-3,4-di(*p*-chlorophenyl)-2,2,5,5-tetramethylhexane *(4)*, since the radicals *(5)* cannot disproportionate, owing to the fact that there are no β-H atoms[1a] and because blocking of the *p*-position leads to formation of only the α,α-dimer *(4)*, but no α,*p*-dimer[5]. In addition, the different thermal stability of the non-chlorinated dimers corresponding to *(4)* and their different conformations were known[8] from X-ray structural[7a] and NMR analysis[7b]. The configurational and conformational analyses of *(4)* could therefore be carried out analogously as in Ref.[6].



The thermolyses of *meso*- and of DL-*(4)* in 1-methylnaphthalene with 10 vol-% thiophenol was investigated kinetically and preparatively. At 300°C, 1-(p-chlorophenyl)-2,2-dimethylpropane is formed in 80% yield from *meso-(4)* and 75% yield from DL-*(4)*. In addition, the stable DL-*(4)* was also formed from *meso-(4)* by cage recombination[9] (*ca.* 10% in 3 halflives). From DL-*(4)* we also obtained *ca.* 3% of a product which was most likely 1,2-di(*p*-chlorophenyl)-3,3-dimethylbutane. Hence, the thermolysis of *(4)* proceeds almost exclusively by cleavage of the central C—C bond; the cage effect does not seriously interfere in the kinetic investigation. The rate of decomposition was determined by measuring the decrease in concentration of *(4)* by GC at 6 temperatures over a range of 50—60°C. The results are listed in Table 1[10].

Table 1. Kinetics of the thermolysis of *meso-(4)* and DL-*(4)* in 1-methylnaphthalene with 10 vol-% thiophenol.

(4)	$\Delta G^{\ddagger}$(300°C) [kcal/mol]	$\Delta H^{\ddagger} \pm \sigma$ [a] [kcal/mol]	$\Delta S^{\ddagger} \pm \sigma$ [a] [cal/mol·K]	k_{rel}(300°C) [b] [s^{-1}]	$T(\tau_{1/2} = 1\ h)$ [c] [°C]
DL	39.4	50.0±0.6	18.5±0.9	≡1.0	301
meso	37.5	47.8±1.0	18.0±1.9	5.5	279

[a] Standard deviation, $r > 0.999$; [b] $\sigma \pm 2.5\%$; [c] temperature for halflife $\tau_{1/2} = 1$ h.

The ratio of the yields is determined by the different strain enthalpy of the diastereomers of *(1)*. As has been demonstrated experimentally[4], the *meso*- and DL-forms of *(1)* with R^1 = *tert*-butyl, R^2 = cyclohexyl, and R^3 = H, differ in strain enthalpy and thermal stability. 1-Cyclohexyl-2,2-dimethylpropyl, or other similarly bulky radicals, should therefore recombine diastereoselectively.

As model compounds for testing this hypothesis we chose the 1-(*p*-chlorophenyl)-2,2-dimethylpropyl radicals *(5)* and

For determination of the diastereoselectivity of the recombination of *(5)*, 1-(*p*-chlorophenyl)-2,2-dimethyl-1-azopropane *(6)* was thermolyzed at 135.2°C in *n*-decane; *(4)* was obtained in 98% yield and, according to GC analysis, consisted of DL-*(4)* and *meso-(4)* in the ratio 1.66±0.05:1. This constitutes the first demonstration of the diastereoselectivity of a radical recombination[11]. For the recombination of *(5)* it is calculated that $\Delta\Delta G^{\ddagger}(135.2°C) = 0.4$ kcal/mol. Attempts to determine the temperature dependence of the yield of diastereoisomers by photolysis of *(6)* have so far failed because of the photolability[12] of *(4)* towards 253.7-nm light. From the activation parameters of the thermolysis of *meso*- and of DL-*(4)* it follows that $\Delta\Delta G^{\ddagger}(135.2°C) \approx 2.0$ kcal/mol for homolytic decomposition. Accordingly DL-*(4)*, with $\Delta\Delta G^{\ddagger} = 2.4$ kcal/mol, is thermodynamically more stable than *meso-(4)*. Since $\Delta S^{\ddagger}$ of the thermolysis of *meso*- and DL-*(4)* is constant within the error of measurement, a difference in strain enthalpy of $\Delta\Delta H = 2.4$ kcal/mol is obtained for the

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[**] Thermolabile Hydrocarbons, Part 9. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 8: *G. Hellmann, H.-D. Beckhaus, C. Rüchardt*, Chem. Ber., in press.

two diastereomers of *(4)*—in good agreement with the result of force field calculations[13] and the known structures[6, 7].

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CAS Registry numbers:
meso-(1), 62678-51-7; DL-*(1)*, 68525-39-3; *(3)*, 68525-40-6; *meso-(4)*, 68525-41-7; DL-*(4)*, 68525-42-8; *(5)*, 68525-43-9; *(6)*, 68525-44-0

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[5] Cf. *e.g. K. S. Skinner, H. S. Hochster, J. M. McBride*, J. Am. Chem. Soc. *96*, 4301 (1974).
[6] Dissertation by *G. Hellmann*, Universität Freiburg 1977, and Part 8 of this series [**]. The DL diastereoisomer decomposes at 300°C with 2.5 kcal/mol higher free activation enthalpy ($\Delta G^{\neq}$) than the *meso* form.
[7] a) *H. J. Lindner, B. Kitschke*, unpublished results. b) *H. Fritz*, unpublished results; the *meso* compound is present in the *anti*-conformer, the DL-compound in the *gauche*-I-structure [8].
[8] *H.-D. Beckhaus, G. Hellmann, C. Rüchardt, B. Kitschke, H. J. Lindner, H. Fritz*, Chem. Ber., in press.
[9] *T. Koenig, H. Fischer* in *J. K. Kochi*: Free Radicals, Vol. 1, p. 157. Wiley-Interscience, New York 1973.
[10] The *p*-chloro substitution leads in *meso-(4)* to 1.1-fold acceleration, but in DL-*(4)* to 1.8-fold acceleration (300°C) relative to the thermolysis of *meso*- and DL-3,4-diphenyl-2,2,5,5-tetramethylhexane [6]. An increase of the dipole moment by substitution is expected only in the case of DL-*(4)* because of its *gauche* conformation [6, 7].
[11] In the dimerization of substituted benzyl radicals the *meso* dimer is often isolated in higher yields as the DL-form. Conclusions on the composition of the crude product, which was not analyzed in any one of the cases, are unreliable. Cf. *P. Gouverneur*, Ind. Chim. Belge *39*, 467 (1974) and [6].
[12] Contrathermodynamically, DL-*(4)* is photochemically more labile than *meso-(4)*.
[13] Using the force field of *Allinger* (1971) and the phenyl parameters of *Mislow* (SET-B), a difference in strain enthalpy of $\Delta\Delta H = 2.9$ kcal/mol [6] was calculated for the non-chlorinated analogues of *meso*- and DL-*(4)*.

Synthesis and Characterization of Liquid-Crystalline Polymers with Cholesteric Phase

By *Heino Finkelmann, Johanna Koldehoff*, and *Helmut Ringsdorf*[*]

We have already demonstrated by means of models that it should be feasible to systematically produce polymers with thermotropic liquid-crystalline phases by analogy with low molecular-weight liquid crystals[1]. The synthetic principle of these polymers lies in a side-chain type linkage to a polymeric backbone of known molecular units leading to a liquid-crystalline phase (mesogenic groups). It is essential that the mesogenic groups be bonded *via* flexible spacer groups (*e.g.* alkyl chains) to the polymer backbone, thus uncoupling the motions of the main and side chains. Nematic and smectic polymers have been synthesized in this way[1].

The synthesis of cholesteric polymers[2] requires that the polymerizable molecules be chiral. Apart from a known copolymeric cholesterol derivative[4], all attempts to polymerize cholesteric monomers led only to smectic polymers[3].

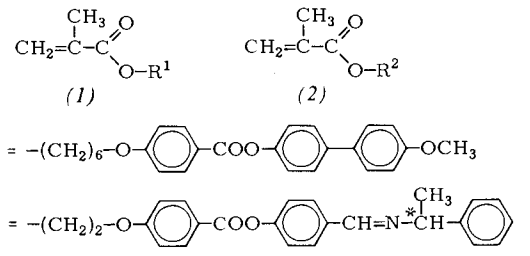
Studies on low molecular-weight liquid crystals have shown that a cholesteric helical structure can be induced in a nematic phase by addition of a chiral compound, even if the chiral component itself is not liquid crystalline[5]. Thus copolymerization of a nematogenic monomer, exhibiting a nematic phase as homopolymer, with a chiral monomer should yield induced cholesteric polymers.

The known biphenylyl benzoate derivative *(1)* served as nematogenic monomer[1]. Its homopolymer exhibits a smectic phase at low temperature in addition to a broad nematic phase (see Table 1). The chiral component *(2)*, which is itself not liquid crystalline as homopolymer, was chosen with the following points in mind:

1) Owing to the amount of chiral (−)-1-phenylethylamine present, small pitches *p* are expected for the cholesteric phase[6] at low concentration of *(2)* in the polymer.

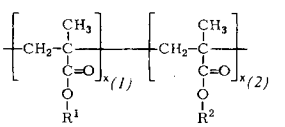
2) In order to minimize perturbation of the nematic phase of polymeric *(1)*, compound *(2)* likewise contains a mesogenic group (phenyl benzoate unit).

3) To ensure random incorporation of monomers *(1)* and *(2)* in the polymer and that their contribution to the polymer corresponds to the composition of the monomeric mixture, the polymerizable groups should have approximately equal reactivities. The chiral monomer *(2)* is therefore also a methacrylate.



Both monomers *(1)* and *(2)* undergo radical polymerization. The phase transitions of the polymers are compiled in Table 1. Studies under a polarizing microscope show that above the glass transition temperature T_G a layer of the polymers located between glass slides spontaneously assumes a cholesteric Grandjean texture. For polymers having $x_{(2)} > 0.17$ this texture is to be seen in the reflection of visible circularly polarized light. It is particularly interesting that the reflecting Grandjean texture remains fixed in the glassy state of the polymer on cooling.

Table 1. Composition, phase transitions, and reflection wavelengths λ_R of the polymers



$x_{(1)}$ [a]	$x_{(2)}$ [a]	Phase transitions [°C] [b]	λ_R [nm] [c]
1.000 (1.000)	—	T_G 60 [d] s 133 n 271 i	∞
0.906 (0.89)	0.094 (0.11)	T_G 70 n* 247 i	1260
0.836 (0.83)	0.164 (0.17)	T_G 73 n* 229 i	712
0.798 (0.79)	0.202 (0.21)	T_G 77 n* 216 i	562
0.753 (0.75)	0.247 (0.25)	T_G 80 n* 203 i	467

[a] Mole fractions based on monomer unit (mole fractions of monomer mixtures given in parentheses).
[b] g = glass transition temperature (from DSC measurements; Perkin-Elmer DSC 1 B); n, n*, s = transitions to the nematic, cholesteric, and smectic phase, respectively; i = isotropic phase.
[c] At $T = 0.9$; $T_{measurement}/T_{clearing\ point}$.
[d] Determined as softening point.

The cholesteric polymers were characterized like conventional cholesteric mixed phases by optical studies on the re-

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flected light of wavelength λ_R as a function of temperature and composition (Fig. 1a). According to *de Vries*[7], λ_R and the pitch p and mean index of refraction $\bar{n}$ are related by $\lambda_R = \bar{n}p$. The reciprocal reflection wavelength ($1/\lambda_R$) is a direct

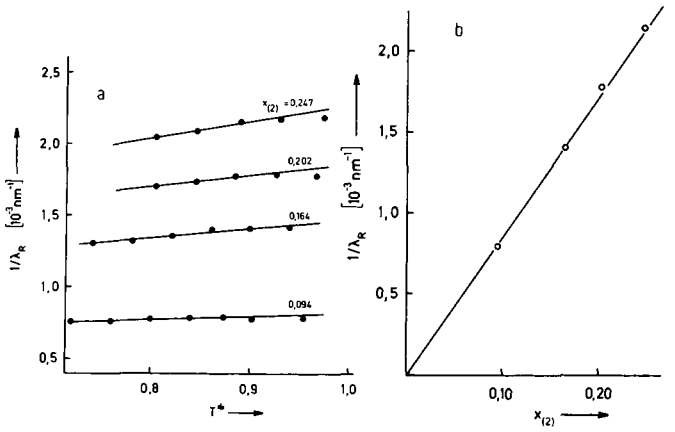


Fig. 1. a) Dependence of the reciprocal of the reflection wavelength $1/\lambda_R$ of cholesteric polymers on the reduced temperature T^* ($T^* = T_{measurement}/T_{clearing\ point}$) and composition (Table 1). b) Dependence of the reciprocal of the reflection wavelength $1/\lambda_R$ on the mole fraction $x_{(2)}$ of the chiral monomer unit *(2)* in the polymer at $T^* = 0.9$. In order to measure the reflection wavelength, the polymeric samples were placed in a layer thickness of *ca.* 20 µm between two plane parallel quartz plates above their glass transition temperature, whereupon the reflecting Grandjean texture immediately appears. The apparent absorption resulting from the reflection was measured in a temperature-controlled measuring cell in a Cary 14 spectral photometer.

measure of helical twisting. $1/\lambda_R = 0$ for nematic phases. As the temperature increases all the polymers show a blue shift of the reflection wavelength, the positive gradient $d(1/\lambda_R)/dT^*$ increasing with increasing amount of chiral component *(2)* in the polymer. Below the glass transition temperature T_G, λ_R is no longer observed to be temperature dependent. The light reflected by the samples investigated is levo-circularly polarized. The polymers accordingly have a cholesteric *l* helix if *(2)* is synthesized from (−)-1-phenylethylamine. The halfwidth of λ_R, determined by measurement of the apparent absorption, lies between 80 and 350 nm for a sample layer thickness of *ca.* 20 µm. The halfwidth increases with increasing temperature and with increasing concentration of the chiral component.

In Figure 1b, $1/\lambda_R$ is plotted as a function of the mole fraction $x_{(2)}$ of the chiral monomer unit. It is seen from this plot (cf. Table 1) that the polymers reflect in the visible region for $0.2 < x_{(2)} < 0.3$. Moreover, it is remarkable that $1/\lambda_R$ is a linear function of $x_{(2)}$ within the limits of experimental accuracy. The optical properties of the polymers thus correspond to those of ideal low-molecular cholesteric mixed systems[6].

The polymers obtained from *(1)* and *(2)* therefore provide the first demonstration that cholesteric polymeric phases can be produced by copolymerization of nematogenic and chiral monomers, by analogy with low molecular-weight cholesteric phases. The optical properties of the polymers resemble those of conventional cholesteric phases. However, it is a novel and characteristic feature of the polymers that the texture reflecting circularly polarized light can be fixed in the glassy state. New applications thus come to mind, such as the production of circular and linear polarization filters and reflectors for light of adjustable wavelength. Uses in display technology and as memory units are also conceivable.

Experimental

Synthesis of the chiral monomer *(1)*: (+)- or (−)-1-phenylethylamine (16 ml) is slowly added dropwise to a hot solution of *p*-hydroxybenzaldehyde (15 g) in toluene (150 ml); the water formed is removed by azeotropic distillation. On completion of reaction, the solution is cooled, and the crude product filtered off. It is recrystallized from ethanol (m. p. 170 °C (dec.)) and transformed into the phenoxide with sodium ethoxide in solution in ethyl alcohol. 4-(4-Chlorocarbonylphenoxy)ethyl methacrylate (50 mmol) in ether (20 ml) is added slowly with stirring at room temperature to sodium 4-(1-phenylethyl)-iminomethylidyne phenoxide (50 mmol). After two hours' stirring the reaction mixture is poured into ether (250 ml), washed with water, and the solvent is removed after drying with Na_2SO_4. Crude *(2)* is recrystallized from ethanol (m. p. 82 °C); *(2)* gives correct analytical values and compatible IR, UV, and ^{1}H-NMR spectra.

Polymerization of *(1)* or *(1)* and *(2)*: The monomer or mixture of monomers is subjected to radical polymerization in 10% tetrahydrofuran solution in the absence of oxygen at 55 °C with 1 mol% of azodiisobutyronitrile as initiator. The polymers are purified by reprecipitating twice from acetone. The ratio of incorporation of the monomers is established by measurement of the optical rotation, and shows the expected agreement with the mixing ratio (see Table 1).

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trans-3,6-Dioxa-9-azatris-σ-homobenzene and *cis*-Epoxyepimino-1,3-cyclohexadiene[**]

By *Eric Francotte, Robert Merényi*, and *Heinz Günter Viehe*[*]

Dedicated to Professor Heinrich Hellmann on the occasion of his 65th birthday

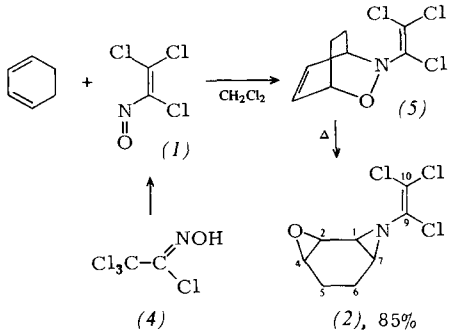
We recently reported the first case of a one step stereospecific epoxyepimination of cyclopentadiene with chloro(nitroso)ethenes[1]. Whereas the addition of nitroso groups to 1,3-dienes is well known, the subsequent rearrangement of the product with stereospecific functionalization of the four sp^2 carbon atoms of the diene constitutes a new reaction, analogous to the rearrangement of endoperoxides to diepoxides[2].

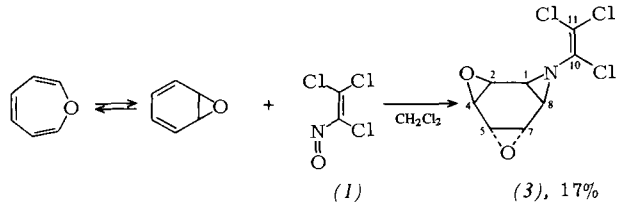
We now report on the stereospecific synthesis of the *N*-trichloroethenyl derivative of *cis*-epoxyepimino-1,3-cyclohexadiene *(2)* and of *trans*-3,6-dioxa-9-azatris-σ-homobenzene *(3)* by reaction of trichloro(nitroso)ethene *(1)* with 1,3-cyclohexadiene and with oxepin[5], respectively. The nitroso compound *(1)* is not stable in pure form at room temperature and

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[**] Aza-Analogy to Singlet Oxygen, Part 2. — Part 1: [1a].

is therefore generated *in situ* from trichloroacetohydroximoyl chloride *(4)*[3].

While oxepin reacts directly with *(1)* to give *(3)*, reaction of *(1)* with 1,3-cyclohexadiene gives cycloadduct *(5)* as intermediate. This thermally labile compound rearranges even at room temperature, and more rapidly on heating, to give *(2)* in quantitative yield.





The structures of the products *(2)* and *(3)* follow from their ^{1}H- and ^{13}C-NMR spectra (see Table 1). In the case of *(2)* the NMR data are comparable with those of the adduct of 1,1-dichloro(nitroso)ethene and cyclopentadiene[1] and with those of the diepoxy-1,3-cyclohexadiene[4].

The vicinal coupling constant $^3J_{1,2}$ in the ^{1}H-NMR spectrum of *(2)* is compatible only with a *cis* configuration. The ^{13}C-NMR spectrum of *(3)* shows six non-identical ring carbon atoms; of the possible stereoisomeric dioxaazatris-σ-homobenzenes[6, 7] *(3)* has the lowest symmetry.

Experimental:

Trichloronitrosoethene *(1)*: A solution of the hydroximoyl chloride *(4)*[3] (2.0 g) in 50 ml of dichloromethane is stirred with 5 g of $NaHCO_3$ for 10 min at room temperature.—IR (CH_2Cl_2): ν = 1610, 1460, 1050, 920, 830 cm^{-1}.—UV/VIS (CH_2Cl_2): λ_{max} = 320 and 740 nm.

8-Trichloroethenyl-*cis*-3-oxa-8-azatricyclo[5.1.0.0^{2,4}]octane *(2)*: A mixture of *(4)*[3] (0.01 mol), cyclohexadiene (0.015 mol) and 4 g of Na_2CO_3 in 50 ml of dichloromethane is stirred for 10 h at room temperature. After evaporation of the solvent, the remaining oil is purified by chromatography [silica gel; cyclohexane/ether (1:1)]; the isomers *(2)* and *(5)* are obtained in variable ratio (overall yield: 85%). *(5)*: colorless liquid; IR ($CHCl_3$): ν = 2980, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.33—1.17 (4H, m), 3.90 (1H, m), 4.57 (1H, m), 6.45 (2H, d of m). *(2)*: white solid, m.p. 64—65 °C; IR ($CHCl_3$): ν = 2990, 1595 cm^{-1}; MS: *m/e* = 239 (M^+), 204, 136, 95, 77, 67.

9-Trichloroethenyl-*trans*-3,6-dioxa-9-azatetracyclo-[6.1.0.0^{2,4}.0^{5,7}]nonane *(3)*: 50 ml of a solution of *(1)*, prepared as above, is added dropwise with stirring at −20 °C to a solution of 2.0 g of the oxepin[5] in dichloromethane. After 6 h at room temperature, the solvent is evaporated off and the residue is purified by column chromatography (silica gel; $CHCl_3$). Yield of *(3)*, m.p. 135—136 °C, 17%. IR ($CHCl_3$): ν = 2990, 1600, 880 cm^{-1}; MS: *m/e* = 253 (M^+), 160, 129, 94, 81, 53.

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Table 1. ^{1}H- and ^{13}C-NMR spectral data of compounds *(2)* and *(3)* in $CDCl_3$ (δ values).

	CH_2—CH_2	CH—CH (*cis*)	CH—CH (*trans*)	CH—CH (N)	CCl=CCl_2	Coupling constants [Hz]
(2)	C-5 C-6	C-2 C-4		C-1 C-7	C-9 C-10	
^{1}H	1.8 1.85	3.45 3.12		2.89 2.55		$^3J_{1,7}$ = 6.8; $^3J_{1,2}$ = 3.2; $^3J_{2,4}$ = 4.0
^{13}C	20.4 18.5	49.0 46.6		40.8 39.6	138.1 107.2	$^1J_7$ = 168.5; $^1J_1$ = 169.5; $^1J_4$ = 177; $^1J_2$ = 179
(3)		C-2 C-4	C-5 C-7	C-1 C-8	C-10 C-11	
^{1}H		3.3	3.45	2.9		
^{13}C		50.6 50.3	47.1 48.0	40.8 39.6	136.6 109.5	^1J(CH—O) = 182, 185, 183, 183 ^1J(CH—N) = 173, 176

Correlation of the Absolute Configuration of Chiral Epoxides by Complexation Chromatography; Synthesis and Enantiomeric Purity of (+)- and (−)-1,2-Epoxypropane[**]

By *Volker Schurig, Bernhard Koppenhöfer*, and *Waldemar Bürkle*[*]

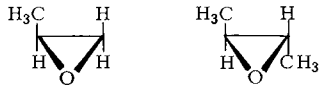
Optically active oxiranes are of interest for the investigation of reaction mechanisms and as synthons in the preparation of chiral natural products[1a]. For use in such studies it is

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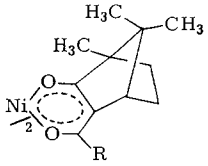
essential that the enantiomeric purity and the absolute configuration of the oxiranes are known with certainty.

We recently described the rapid and quantitative resolution of the enantiomers of the racemic oxiranes 1,2-epoxypropane *(1)* and *trans*-2,3-epoxybutane *(2)* by complexation chromatography on optically active nickel(II) bis(3-trifluoroacetyl-1*R*-camphorate) *(3a)* in squalane solution as selective stationary phase[2].



S-*(1)*

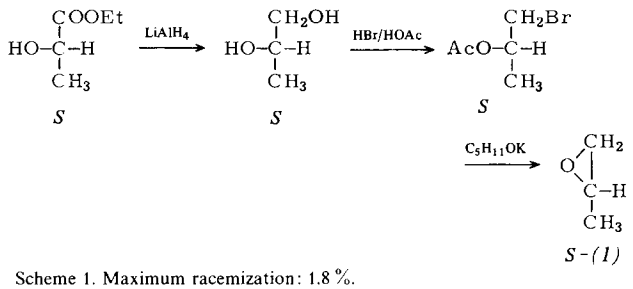
2*S*, 3*S*-*(2)*



(3a), R = CF_3
(3b), R = $CF_2CF_2CF_3$

We have now found that replacement of the trifluoroacetyl group by a heptafluorobutyryl group *(3b)* increases the capability of enantiomer differentiation of the separating phase and leads to the greatest separation factors so far observed for chiral recognition by enantiospecific "one point" coordination [*(1)*, $\alpha = 1.24$; *(2)*, $\alpha = 1.43$, 50°C]. We describe here the use of this method for the determination of enantiomeric purity, for the extrapolation of the optical rotation of the *pure* enantiomer, and for the correlative determination of configuration using as example *R*- and *S*-epoxypropane.

(−)-*S*-*(1)* was synthesized from ethyl (−)-*S*-lactate according to the method of *Golding et al.*[1b] (Scheme 1).



Scheme 1. Maximum racemization: 1.8%.

The complexation chromatogram (Fig. 1, left) of the reaction product, $[\alpha]_D^{20} = -14.14°$ (neat)[3], shows 1.8% of the *R*-antipode corresponding to an enantiomeric purity of 96.4% for (−)-*S*-*(1)*. This yielded the following corrected optical rotations for pure *S*-*(1)*: $[\alpha]^{20} = -14.65° \pm 0.05°$ (D); −15.15° (578); −16.70° (546); −23.35° (436); −26.28° (365); $[\alpha]_D^{16} = -14.90° \pm 0.05°$. The lower values reported in the literature thus correspond to samples of lower enantiomeric purity[4].

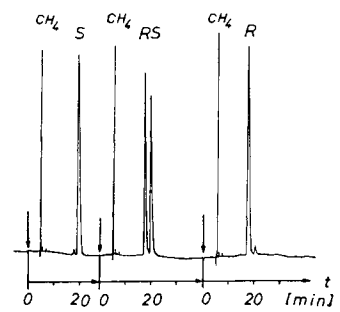
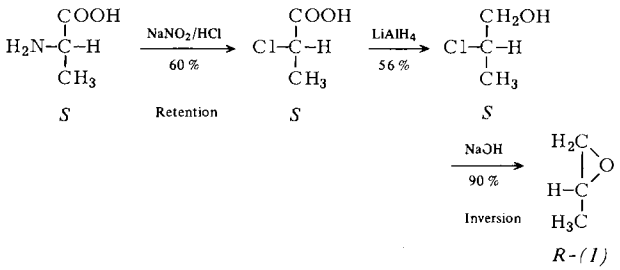


Fig. 1. Resolution of *(1)* by complexation gas chromatography on 1*R*-*(3b)* [0.13 *m* (monomer) in squalane] at 70°C. Column: 100 m × 0.5 mm nickel capillary, carrier gas: 3.8 ml/min N_2, split 1 : 50. Left (−)-*S*-*(1)*; center: racemic *(1)*; right: (+)-*R*-*(1)*.

In the case of the (+)-*R*-*(1)* antipode we have worked out a productive method for the synthesis of chiral 1,2-epoxides of high optical purity from naturally occurring L(*S*)-amino acids by a combination of classical reaction steps (Scheme 2).



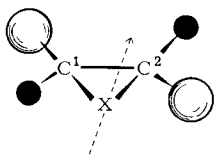
Scheme 2. Maximum racemization only 2.7% despite twofold direct substitution at the asymmetric carbon atom.

(+)-*R*-*(1)* was synthesized from L-alanine *via* *S*-2-chloropropionic acid[5] and *S*-2-chloro-1-propanol. The complexation chromatogram (Fig. 1, right) showed 2.7% of the *S*-antipode, corresponding to an enantiomeric purity of 94.6% for (+)-*R*-*(1)*. These investigations also make it possible to draw conclusions on the stereochemical course of the reaction of L-alanine with aqua regia (!) to give 2-chloropropionic acid[6]. The reaction must proceed with at least 89.4% retention, since (+)-*(1)*, $[\alpha]_D^{20} = +11.25°$ (neat), prepared *via* this route contains only 10.6% of the *S*-enantiomer, corresponding to 78.8% enantiomeric purity. The corrected optical rotation for (+)-*R*-*(1)* is thus $[\alpha]_D^{20} = +14.6° \pm 0.3°$.

It follows from Figure 1 that one of the enantiomers of 1,2-epoxypropane is formed according to Scheme 1, the other enantiomer according to Scheme 2. Thus, the configuration of L-alanine and L-lactic acid have been assigned *via* an independent route[7].

The *S*-*(1)* enantiomer is eluted later than the *R*-antipode on the nickel complex derived from (+)-1*R*-camphor. *Gil-Av et al.* were the first to correlate the absolute configuration of chiral substrates from the chromatographic retention behavior on an optically active stationary phase of defined chirality[8]. We extend this method, which does not necessitate knowledge of the absolute configuration of the separating phase, to the enantiospecific ligand-metal coordination interaction and we formulate a *quadrant rule* for the retention behavior of chiral three-membered ring heterocycles of structure *(4)* on (+)-*(3b)* as stationary phase, with (−)-*S*-*(1)* as reference compound:

When the molecule is viewed from the donor heteroatom in the direction of the horizontal C—C bond, the absolute configuration of the enantiomer eluting *later* is that in which the bulkier group(s) is(are) situated on the upper left at C-1 and/or lower right at C-2.



X = NH, O, S *(4)*

According to this rule, *e.g.*, the enantiomer of 1,2-epoxybutane ($\alpha = 1.11$, 50°C) eluting later on (+)-*(3b)* would be assigned the *S*-configuration. As expected, in the case of *trans*-2,3-epoxybutane *(2)* the 2*S*,3*S*-enantiomer[9] exhibits stronger interaction than the *R*-antipode with (+)-*(3b)* and is thus more strongly retarded.

As a further consequence of the rule, it can be predicted that chiral unsymmetrically substituted 1,1- or 1,2-*cis* derivatives ought to show only a slight enantiomeric resolution on *(3)*, compared to monosubstituted compounds, whereas 1,2-disubstituted *trans*-isomers ought to exhibit greater enantiomeric resolution. Indeed, it is found that the difference in free association enthalpy of the enantiomers of *(2)* ($\Delta_{S,R}(\Delta G) = -0.23$ kcal/mol, 323 K) on (+)-*(3b)* is almost double that observed in the case of the enantiomers of *(1)* ($\Delta_{S,R}(\Delta G) = -0.14$ kcal/mol, 323 K).

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S-(1), 16088-62-3; *R-(1)*, 15448-47-2; ±-*(1)*, 16033-71-9; *(2)*, 63864-69-7; *(3b)*, 68457-34-1; ethyl(−)-*S*-lactate, 687-47-8; *S*-1,2-propanediol, 4254-15-3; 1-bromopropan-2-yl acetate, 39968-99-5; L-alanine, 56-41-7; *S*-2-chloropropionic acid, 29617-66-1; *S*-2-chloro-1-propanol, 19210-21-0

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[9] 2*S*,3*S*-Epoxybutane (2*S*,3*S*-*(2)*) was prepared from 2*R*,3*R*-tartaric acid *via* 2*R*,3*R*-threitol ditosylate; *B. Koppenhöfer, V. Schurig*, unpublished work; cf. also *K. Mori, S. Tamada, M. Matsui*, Tetrahedron Lett. *1978*, 901.

Structure of the First Open-Chain Diorganotin Chalcogenide[**]

By *Heinrich Puff, Anne Bongartz, Rolf Sievers*, and *René Zimmer*[*]

In previous X-ray crystallographic investigations on diorganotin chalcogenides either six-membered puckered[1] or four-membered planar[2] ring structures have been found. Besides these cyclic species we have also been able to isolate some compounds in modifications whose properties such as very low solubility, high and indefinite melting point, and special features in the vibrational spectrum[3] would indicate a polymeric structure. We have now found that colorless single crystals of polymeric diisopropyltin sulfide are formed if the initially low-molecular form of the product[4] obtained according to

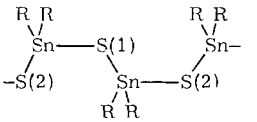
$$i\mathrm{Pr_2SnCl_2} + \mathrm{Na_2S} \rightarrow 2\,\mathrm{NaCl} + i\mathrm{Pr_2SnS}$$

is allowed to stand under solvent (DMF). The new modification crystallizes orthorhombically (space group $Pna2_1$-C_{2v}^9; $a = 16.319$, $b = 9.455$, $c = 5.988$ Å) with four formula units $(C_3H_7)_2SnS$ in the unit cell.

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The X-ray structure analysis[5] ($R = 0.042$) showed that tin and sulfur atoms are coupled alternatively in a planar chain in the direction of the *c*-axis[6].



Bond length	[Å]	Angle	[°]
Sn—S(1)	2.45	S—Sn—S	100.7
Sn—S(2)	2.40	Sn—S—Sn	105.6
Sn—C	2.17, 2.19	C—Sn—C	119.9

The SSnS angle (100.7°) in the chain lies between the values observed in six-membered[1] (106.1—108.7°) and four-membered rings[2] (94.0—94.3°). A comparison of the $(R_2SnX)_n$ structures so far investigated shows that the ring size in the *cyclo* forms and the relative stability of the *cyclo* and *catena* modifications are determined more by electronic effects of the organic groups R than by spatial requirements.

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i-Pr_2SnS, 68525-33-7; *i*-Pr_2SnCl_2, 38802-82-3; Na_2S, 1313-82-2

[1] *H. J. Jacobsen, B. Krebs*, J. Organomet. Chem. *136*, 333 (1977); *B. Menzebach, P. Bleckmann, ibid. 91*, 291 (1975); *R. Hundt*, Dissertation, Universität Bonn 1973.
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[3] The bands (IR, Raman) assigned to SnS vibrations in the polymeric diorganotin sulfides are markedly shifted to smaller wavelengths in comparison to the ring-shaped molecules and also show different splitting.
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[5] Four-circle diffractometer CAD4; program system X-RAY, IBM/370-168 computer, Regionales Hochschulrechenzentrum der Universität Bonn.
[6] A similar chain-form was found in the case of $K_2SnS_3 \cdot 2H_2O$: *W. Schiwy, C. Blutau, D. Gäthje, B. Krebs*, Z. Anorg. Allg. Chem. *412*, 1 (1975).

Ozone Cleavage of Olefins with Formation of Ester Fragments[**]

By *Joachim Neumeister, Helmut Keul, Mahendra Pratap Saxena*, and *Karl Griesbaum*[*]

Despite the manifold analytical and preparative applicability of the ozone cleavage reaction[1], there is as yet no method available which upon ozonolysis of 1,2-disubstituted ethylenes *(1)* affords directly the corresponding ester fragments *(5)*. We have now found that this is possible, however, if the ozonolysis of olefins *(1)* is carried out in an alcohol (R^1OH) in the presence of anhydrous hydrochloric acid.

The olefin *(1)* is ozonized at low temperatures (−50° to −70°C) until the double bonds are totally cleaved. The mixture is then allowed to warm to room temperature without further addition of ozone. During this time, an exothermic reaction occurs and concurrently the mixture becomes free of peroxide. Finally, ozone treatment is continued at −10° to +20°C until formation of ester is completed.

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GLC analysis of the crude reaction products revealed yields of over 90 % of the corresponding esters. The yields of isolated esters were lower (62—85 %), this being partly due to difficulties in the separation of the esters *(5)* from the excess alcohol employed (Table 1).

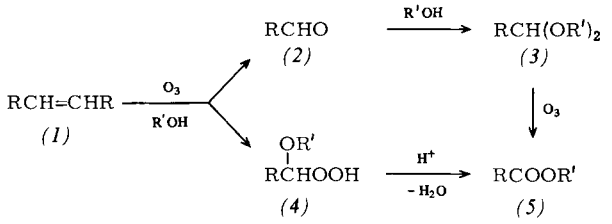


Table 1. Yields of esters on ozonolysis of olefins in the presence of HCl/R'OH [a].

Olefin *(1)*	Ester *(5)*	Yield [%]
4-Octene	$CH_3CH_2CH_2COOCH_3$	65
Stilbene	$C_6H_5COOCH_3$	72
Cyclopentene	$CH_3OOC(CH_2)_3COOCH_3$	78
Cyclohexene	$CH_3OOC(CH_2)_4COOCH_3$	85
Cyclooctene	$CH_3OOC(CH_2)_6COOCH_3$	80
Cyclodecene	$CH_3OOC(CH_2)_8COOCH_3$	62
[b]	$C_2H_5OOC(CH_2)_8COOC_2H_5$	69
[c]	$C_3H_7OOC(CH_2)_8COOC_3H_7$	80
1,5-Cyclooctadiene	$CH_3OOC(CH_2)_2COOCH_3$	64
Norbornene	Dimethyl 1,3-cyclopentane dicarboxylate (*cis*:*trans* = 9:1)	83

[a] Unless otherwise stated R' = CH_3. [b] R' = C_2H_5. [c] R' = *n*-C_3H_7.

Model reactions using selected olefins have shown that the reaction apparently proceeds *via* the following steps: Initially, the Criegee-fragments *(2)* and *(4)* are formed[2]. Acid-catalyzed dehydration of the alkoxy hydroperoxide *(4)* affords in an exothermic reaction the ester *(5)*[3], and at the same time aldehyde *(2)* is converted into the acetal *(3)*. On further treatment with ozone, *(3)* is finally converted into ester *(5)*[4].

Further work is underway concerning the course of the reaction, possible side-reactions, and the scope of this method with respect to variation of olefin and alcohol.

Typical Procedure

A mixture of 8.2 g (0.1 mol) of cyclohexene and 87 ml of a *ca.* 1 M solution of anhydrous hydrochloric acid in methanol was ozonized at −78 °C until ozone left the reaction vessel (KI-trap). The mixture was then flushed with nitrogen and subsequently allowed to warm. At approx. 0 °C an exothermic reaction set in (the mixture was cooled in an ice-bath so that the temperature did not exceed 35 °C). When the mixture was free of peroxide, ozone treatment was continued for 24 h at 0 °C. Then the mixture was flushed with nitrogen, refluxed for 3 h, and cooled to room temperature. Solid sodium bicarbonate was added, the mixture filtered, and the filtrate concentrated by evaporation at 35 °C/15 torr. The liquid residue was dissolved in 50 ml of ether, washed with 3 × 20 ml of water, dried over sodium sulfate, and the ether distilled off. Distillation of the residue (15.9 g) afforded dimethyl adipate, b.p. of 88—90 °C/0.3 torr (purity 98.4 %); yield 14.8 g (85.1 %).

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Demonstration of Diastereomeric Electron-Donor-Acceptor Complexes by ^{1}H-NMR Spectroscopy[**]

By *Albrecht Mannschreck*, *Peter Roza*, *Hans Brockmann Jr.*, and *Thorsten Kemmer*[*]

Electron-donor-acceptor (EDA) complexes can frequently be detected in the UV/VIS spectrum by a band at long wavelength. This is rendered more difficult if the band is situated close to the absorption of a component. The change of NMR shifts can also provide proof of EDA complexes[1]; however, further influences upon the δ values, *e. g.* diamagnetic anisotropies, have to be taken into account besides genuine charge-transfer effects. In the case of *chiral* components, chiroptical properties[2] as well as ^{1}H-NMR signal splitting[3] by diastereomeric complexes represent further possibilities of investigation. The latter phenomenon may in principle be caused by all types of molecular association, although *Pirkle et al.*[3a] were the only ones to discuss such signal splittings in terms of an EDA interaction. *Pirkle et al.* suggested an EDA contribution besides hydrogen bonds for the complexation of dinitrophenyl compounds with 1-(1-naphthyl)ethylamine or 1-(9-anthryl)-2,2,2-trifluoroethanol. We have now succeeded in detecting diastereomeric EDA complexes unequivocally by NMR spectroscopy.

For this purpose we chose components for association which are available in optically active and in racemic form and for which, in addition, a high tendency for complexation was to be expected[4].

The fluorene derivative (*R*)-*(2)* which is used for preparative and analytical separation of enantiomers[5] served as a π-acceptor. The carbazole derivatives[6] (*RS*)-*(1)*, (*RS*)-*(3)*, (*RS*)-*(4)*, and (*RS*)-*(5)* were chosen as π-donors. The charge-transfer band of such EDA complexes around 500 nm overlaps with the absorption of *(2)* at longest wavelength (λ_{max} = 355 nm, lgε = 4.2, $CHCl_3$)[2a]. The ^{1}H-NMR signals of H-1, H-6, and H-8 in (*R*)-*(2)* as well as of H-4/H-5 in (*RS*)-*(2)* are shifted to *higher* field by 0.1 to 0.3 ppm when the mixture in [D_6]-acetone is cooled from +25 °C to −68 °C (Fig. 1, Table 1). At the same time, the *H*—C—CH_3 quartet of (*RS*)-*(1)* moves to *lower* field by 0.13 ppm, while all other C—H signals (except the non-analyzed absorptions of further ring protons in (*RS*)-*(1)*) approximately retain their positions. This behavior is compatible with equilibria shifted in favor of the association complexes by lowering the temperature, the shifts[4] being mainly due to the diamagnetic anisotropies of the two aromatic

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[**] Application of NMR Spectroscopy of Chiral Associates, Part 7. This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie. Some of the measurements were carried out by Dr. *T. Burgemeister* and *H.-H. Henschel*. We are grateful to Dr. *G. Becher* and Dr. *M. Holík* for discussions.—Part 6: *M. Holík*, *A. Mannschreck*, Org. Magn. Reson., in press.

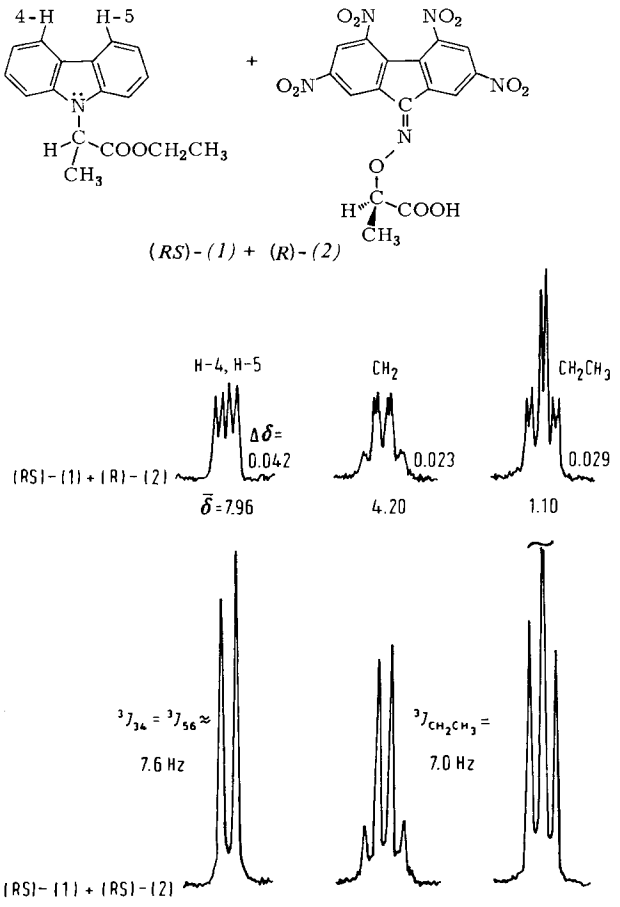


Fig. 1. Some ^{1}H-NMR signals (90 MHz, PFT method) of the π-donor (*RS*)-*(1)* in [D_6]-acetone at −68 °C in the presence of 1.15 equivalents of the π-acceptor (*R*)-*(2)* (top) and (*RS*)-*(2)* (bottom). $\bar{\delta}$: Mean shift of corresponding protons in (*R*)-*(1)* and (*S*)-*(1)*. $\Delta\delta$: Difference of shifts of corresponding protons in (*R*)-*(1)* and (*S*)-*(1)*. See Table 1 for details.

systems. The existence of the diastereomeric complexes[7] (*R*)-*(2)*···(*R*)-*(1)* and (*R*)-*(2)*···(*S*)-*(1)* follows from the additional splittings of several absorptions of (*RS*)-*(1)* at −68 °C, which are diminished by raising the temperature. As expected[3], these shift differences ($\Delta\delta$ in Fig. 1, top, and in Table 1) disappear by averaging, if the *racemic* compound (*RS*)-*(2)* is used instead of the optically active one (Fig. 1, bottom).

tation[8] of the components in the complex, which means a change in the shift differences $\Delta\delta$.—As expected, some signals of the fluorene derivative (*RS*)-*(2)* are split (Fig. 2), if the carbazole (*R*)-*(3)*[6] is used as the optically active component.

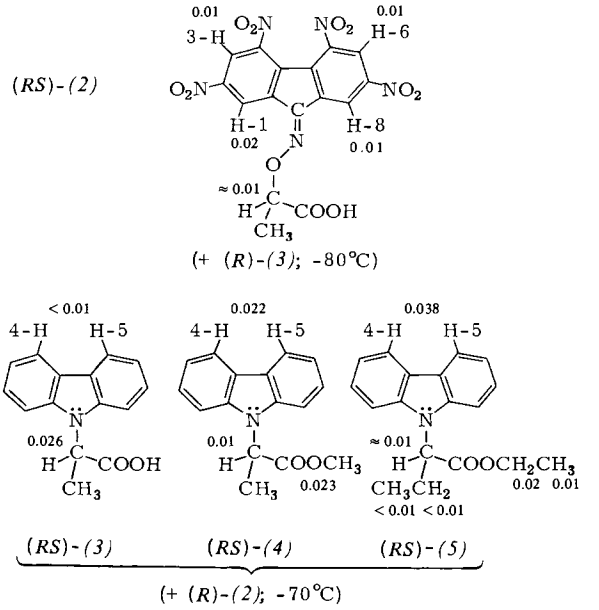


Fig. 2. π-Acceptor (*RS*)-*(2)* and π-donors (*RS*)-*(3)*, (*RS*)-*(4)*, and (*RS*)-*(5)*. The numbers are $\Delta\delta$ values in [D_6]-acetone, *i.e.* differences between the ^{1}H-NMR shifts of the (*R*)- and the (*S*)-enantiomer for the given combinations. The molar ratio of optically active compound to (*RS*)-substrate is 1.1 : 1.

The above association complexes might be caused not only by the EDA interaction, but also by hydrogen bonds of carbonyl groups. This possibility is excluded when two carboxylic *esters* are paired. Thus, the ester (*RS*)-*(1)* behaves largely analogously in the presence of the carboxylic acid (*R*)-*(2)* (Fig. 1 and Table 1) and in the presence of its methyl ester[9]; in addition, the $\Delta\delta$ values for both mixtures are very similar. These findings, combined with literature statements[10], enable us to conclude, that the EDA interaction, and not a possible hydrogen bond, is of decisive importance for the relative orientation of the partners in the above complexes of esters with acids.

The phenomenon described in this paper can serve to demonstrate the presence of EDA complexes and, if optimized,

Table 1. ^{1}H-NMR signals of a mixture of (*RS*)-*(1)* and 1.15 equivalents (*R*)-*(2)* in [D_6]-acetone at −68 °C. δ: Chemical shifts; in the case of (*RS*)-*(1)*, δ represents the *averaged* shift of (*R*)-*(1)* and (*S*)-*(1)*. $\Delta\delta$: Difference of shift of corresponding protons in (*R*)-*(1)* and (*S*)-*(1)*.

	(*RS*)-*(1)*						(*R*)-*(2)*				
δ	7.96	7.5—6.8	5.85	1.78	4.20	1.10	9.36	8.97	8.79, 8.65	5.34	1.85
J [Hz]	$J_{34}=J_{56}\approx 7.6$	?	7.0	7.0	7.0	7.0	$J_{13}=2.1$	$J_{13}=2.1$	$J_{68}=2.1$	7.0	7.0
$\Delta\delta$	0.042	?	0.01	[a]	0.023	0.029	—	—	—	—	—
Assignment	H-4, H-5 [b]	H-1, H-2, H-3 H-6, H-7, H-8	H—C—CH_3	H—C—CH_3	CH_2—CH_3		H-1 [c]	H-3	H-6, H-8	H—C—CH_3	H—C—CH_3

[a] This value cannot be determined precisely because the H—C—CH_3 absorption of (*R*)-*(2)* is close; $\Delta\delta$ is probably <0.01. [b] Assignment analogous to carbazole and 9-methylcarbazole, the protons of which were assigned *via* ^{13}C-NMR shifts and selective $^{13}C\{^1H\}$ decoupling experiments. We are grateful to Dr. *L. Ernst*, Braunschweig-Stöckheim, for these measurements. Cf. *P. J. Black, M. L. Heffernan*, Aust. J. Chem. *18*, 353 (1965). [c] Assignment analogous to *H. Paulsen, K. Todt, H. Ripperger*, Chem. Ber. *101*, 3365 (1968), and references cited therein.

The comparison of the $\Delta\delta$ values of the carbazole derivative (*RS*)-*(1)* (Table 1) with those of (*RS*)-*(3)*, (*RS*)-*(4)*, and (*RS*)-*(5)* (Fig. 2) shows that the spatial positions of H-4 and H-5 in the complexes with (*R*)-*(2)* are changed by modifications of the distant substituent in the 9-position of the carbazole nucleus. The spatial position of the N—C—*H* atom is apparently changed to a lesser extent. The modification of a substituent probably brings about a change in relative orientation to measure the enantiomeric purity. Independently, we aim to understand the δ- and $\Delta\delta$-values in terms of the orientation of the components in solution.

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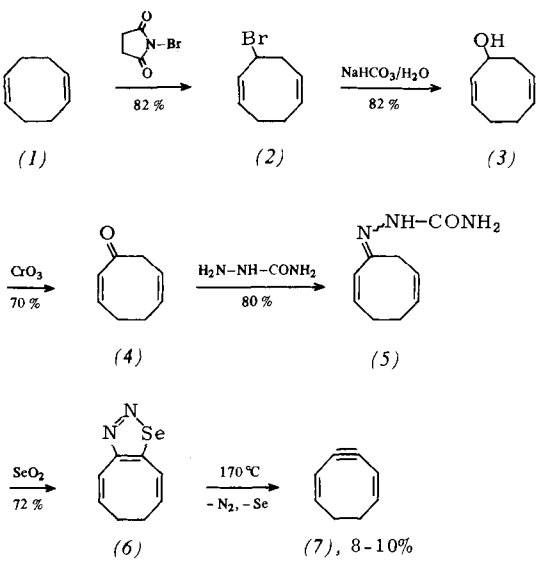
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[7] EDA complexes consisting of more than two components would not change the conclusions drawn.
[8] Cf. *H. A. Staab, V. Taglieber*, Chem. Ber. *110*, 3366 (1977), and earlier papers.
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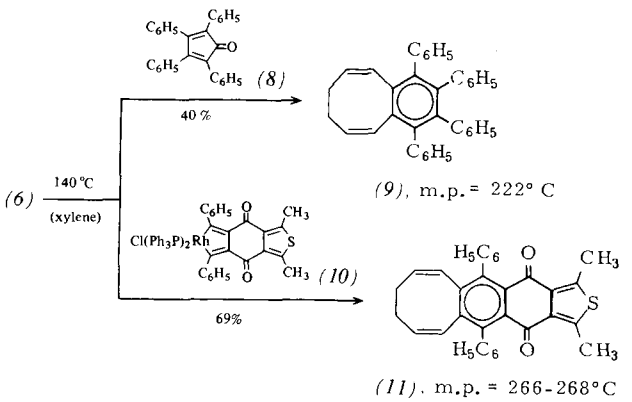
1,5-Cyclooctadien-3-yne—A Novel, Highly Reactive C_8H_8 Hydrocarbon[**]

By *Herbert Meier, Toni Echter*, and *Hermann Petersen*[*]

To the prominent family of C_8H_8 hydrocarbons belong the well-known members styrene, cyclooctatetraene, cubane, barrelene, semibullvalene, and 1,5-cyclooctadiyne. We have now succeeded in isolating a new isomer, namely the highly strained and thus highly reactive eight-membered ring compound 1,5-cyclooctadien-3-yne *(7)*.

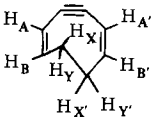


In the synthesis of *(7)* the route to *(4)* described by *Cantrell* and *Solomon*[1] has been shortened by one step and the yield of *(4)* vastly improved. 1,2,3-Selenadiazole *(6)* is accessible *via* the semicarbazone *(5)*[2]; thermolysis of *(6)* over copper powder in an atmosphere of N_2 leads to *(7)*. As soon as reaction sets in, the initial pressure is reduced from 70 to 1 torr and the volatile fragmentation product *(7)* is frozen out in a cold trap with liquid nitrogen. *(7)* can be trapped *in situ* in much higher yields; besides tetracyclone *(8)*, which has proven suitable for Diels-Alder cycloaddition, rhodium complexes of type *(10)*[3] are particularly efficient trapping reagents:



The cyclooctadienyne *(7)* can be stored in the solid state in the absence of oxygen. Above the melting point at *ca.* −15°C it begins to decompose. When dissolved in $CDCl_3$ its halflife at 27°C is about 2 h. The lifetime of *(7)* is not only limited by di- and oligomerizations, as expected for strained cycloalkynes, but also by an intramolecular process with a low energy barrier: The transformation into cyclooctatetraene can be explained in terms of two thermally allowed, suprafacial 1,5 H-shifts. A mechanistic alternative is intramolecular $[\pi 2 + \sigma 2 + \sigma 2]$ cycloaddition, a novel type of reaction with σ_{CH} bonds, reminiscent of the diimine reduction of olefins[4].

The extremely high degree of ring strain *(7)* is also manifested in the spectroscopic properties. The ^{13}C-NMR spectrum shows four signals: The saturated C-atoms absorb at $\delta = 32.6$, the olefinic C-atoms at $\delta = 152.0$ and 112.7; for the sp centers an extremely large downfield shift of $\delta = 116.3$ is observed. From these data an energy of geometrical strain[5] of *ca.* 18 kcal/mol is estimated (cyclooctyne has a geometrical strain energy of 12 kcal/mol). From the data it also follows that the molecule must have a symmetry axis or a symmetry plane (C_2 or C_s conformation). From the ^1H-NMR spectrum recorded at −40°C it can be concluded that no rapid ring inversion takes place under these conditions (AA'BB'XX'YY' system). According to a simple force-field calculation, the C_s conformation ought to have a higher energy than the C_2 conformation. Analysis of the ^1H-NMR spectrum is fully consistent with a C_2 conformation.



(7) (C_2)

We thus have the relatively rare case of a chiral hydrocarbon without an asymmetric C-atom. At room temperature the X and Y parts of the spectrum (at $\delta = 1.2$ and 2.9, respectively) broaden and lose their fine structure; the AB part remains practically unchanged [$\delta = 5.8$ (H_A), 6.6 (H_B)]. The coalescence point is reached at 60°C, corresponding to a $\Delta G^{\neq}$ of *ca.* 16 kcal/mol for the transition state. At room temperature, 1,5-cyclooctadiene and 1,3,5-cyclooctatriene exhibit rapid ring inversion; the coalescence temperature lies, *e.g.* for the triene, at −136°C[6]. Replacement of a CC single or double bond by a triple bond leads to a rigid conformation owing to increased ring strain. The coalescence temperatures of cyclooctyne and the cyclooctenynes[7], however, lie below room temperature. Only introduction of the second double bond into the eight-membered ring alkyne effects freezing-in of ring inversion. If the double bond is replaced by annelated benzene units, then the effect is enhanced[6, 8].

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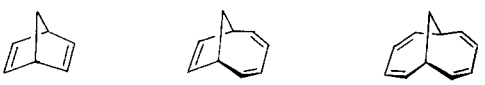
CAS Registry numbers:
(1), 111-78-4; *(2)*, 23346-40-9; *(3)*, 10017-18-2; *(4)*, 1460-21-5; *(5)*, 68344-44-5; *(6)*, 68344-45-6; *(7)*, 68344-46-7; *(8)*, 479-33-4; *(9)*, 68344-47-8; *(10)*, 56397-59-2; *(11)*, 68344-48-9

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1,6-Dimethylbicyclo[4.4.1]undeca-2,4,7,9-tetraene—A Higher Vinylog of Norbornadiene

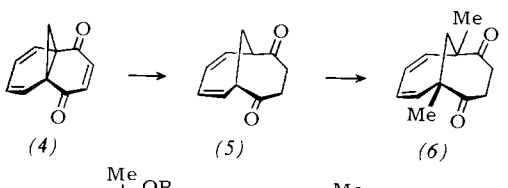
By *Jürgen Frank, Wolfram Grimme*, and *Johann Lex*[*]

The homoconjugation between the unsaturated bridges in norbornadiene *(1)* and bicyclo[4.2.1]nonatriene *(2)* is revealed in the PE-spectroscopic[1a] as well as the chemical[1b, 1c] behavior of the two compounds. A corresponding interaction is to be expected in the next higher vinylog of this series, the previously unknown bicyclo[4.4.1]undecatetraene *(3)*.

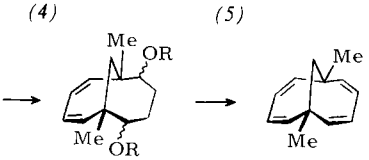


(1) *(2)* *(3)*

Actually, the fully-conjugated skeleton, *i.e.* 1,6-methano[10]annulene[2] has been known for some 15 years, but of its dihydro derivatives only the 1,2-[3a] and the 2,5-isomer[3b] have so far been reported. The elusiveness of the structure *(3)* with two sp^3 hybridized bridgeheads might be due to the particularly large increase in strain (estimated as 2×6.8 kcal/mol[4]) on going from 1,6-methano[10]annulene to *(3)*. Hence, owing to the easy double bond shift to be expected in *(3)* we have synthesized the methyl-stabilized title compound *(8)*.



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



(7a), R = H *(8)*
(7b), R = O_2SMe

The tricyclic "2,5-quinone" *(4)*[5a] is reduced by zinc dust in 95% acetic acid at room temperature to the bicyclic 2,5-dione *(5)*[5b] (92% yield), which can be methylated at both bridgeheads with methyl iodide to give *(6)* (42%) *via* the bisenolate generated with lithium diisopropylamide in tetrahydrofuran at 0°C (for physical data see Table 1). Reaction of *(6)* with sodium tetrahydroborate in methanol affords the stereoisomeric diols *(7a)* (62%) as a 3:2 mixture of a *cis*-isomer of unknown configuration and the *trans* compound (m.p. 157°C). On esterification of the mixture with methanesulfonyl chloride in pyridine the bismethanesulfonates *(7b)* are obtained (88%), which are then allowed to react with potassium *tert*-butoxide in ice-cold dimethyl sulfoxide. Low-pressure chromatographic separation (silica gel, pentane) of a pentane extract of the reaction mixture at −10°C affords the title compound *(8)* (22%) as a product of twofold elimination. The NMR spectra (Table 1) confirm its C_{2v} symmetry; the UV spectrum shows a bathochromic shift of about 17 nm compared to that of 1,3-cycloheptadiene, which can be explained in terms of a homoconjugation or planar fixation of the diene units.

Table 1. Physical data of compounds *(5)*, *(6)*, *(8)*, *(9)*, *(10)*, and *(11)*. The ^{1}H-NMR spectra were recorded at 90 MHz in $CDCl_3$ [*(8)* and *(9)* in CCl_4].

(5), m.p. 35°C; ^{1}H-NMR: $\delta = 6.10$ (AA'BB', H-7, 8, 9, 10), 3.70 (m, H-1, 6), 2.63 (AA'BB', H-3, 3', 4, 4'), 2.33 (tripletted AB, $\Delta_\nu = 31.6$ Hz, $J = 16.5$ Hz, H-11, 11')

(6), m.p. 52°C; ^{1}H-NMR: $\delta = 6.1$–5.5 (AA'BB', H-7, 8, 9, 10), 3.1–2.4 (AA'BB', H-3, 3', 4, 4'), 2.10 (AB, $\Delta_\nu = 25.8$ Hz, $J = 15$ Hz, H-11, 11'), 1.28 (s, 6H, CH_3)

(8), m.p. 18°C; ^{1}H-NMR: $\delta = 5.43$ (narrow AA'BB', 8 olefin-H), 2.53 (s, 2H, CH_2), 1.25 (s, 6H, CH_3); ^{13}C-NMR ($CDCl_3$, 20 MHz): $\delta = 140.81$ (C-2, 5, 7, 10), 122.31 (C-3, 4, 8, 9), 50.77 (C-11), 44.39 (C-1, 6), 31.60 (2C, CH_3); UV (hexane): $\lambda_{max} = 245$ nm ($\varepsilon = 4200$), 255 (5000), 265 (3600)

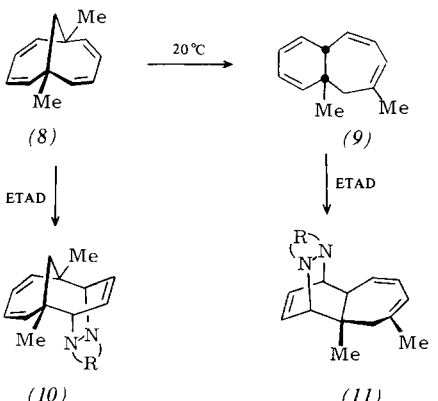
(9), ^{1}H-NMR: $\delta = 5.8$–5.2 (m, 7 olefin-H), 2.72 (t, H-1), 2.05 (AB, $\Delta_\nu = 72.7$ Hz, $J = 15$ Hz, H-6, 6'), 1.90 (s, 3H, 5-CH_3), 1.03 (s, 3H, 7-CH_3); UV (cyclohexane): $\lambda_{max} = 236$ nm ($\varepsilon = 10000$), 257 (6600) sh

(10), m.p. 152°C; ^{1}H-NMR [a]: $\delta = 6.13$ (AA'XX'-half-spectrum, H-3, 4), 5.7 (narrow m, H-7, 8, 9, 10), 4.50 (AA'XX' half-spectrum, H-2, 5), 3.62 (q, 2H, CH_2CH_3), 2.02 (AB, $\Delta_\nu = 35.7$ Hz, $J = 13.5$ Hz, 2H, CH_2), 1.27 (t, 3H, CH_2CH_3), 1.25 (s, 6H, CH_3); MS: $m/e = 299$ (M^+)

(11), m.p. 137°C; ^{1}H-NMR [b]: $\delta = 6.42$ (t, H-9, 10), 5.87 (m, H-2, 3, 4), 4.67 (m, H-11), 4.30 (t, H-8), 3.87 (q, 2H, CH_2CH_3), 2.23 (AB, $\Delta_\nu = 104.5$ Hz, $J = 13.5$ Hz, H-6, 6'), 1.95 (s, 3H, 5-CH_3), 1.57 (m, H-1), 1.20 (t, 3H, CH_2CH_3), 1.00 (s, 3H, 7-CH_3); UV (ethanol): $\lambda_{max} = 248$ nm ($\varepsilon = 10300$)

[a] Molecular skeleton numbered analogously to *(8)*.
[b] Molecular skeleton numbered analogously to *(9)*.

Reaction of *(8)* with 4-ethyl-1,2,4-triazolinedione (ETAD) in acetone at 0°C affords the monoadduct *(10)* (67%); the bicyclic compound thus reacts like its next lower vinylog *(2)*[6] and not analogously to norbornadiene *(1)* across the 2,10 positions.



(8) *(9)*
(10) *(11)*
R = –CO–NEt–CO–

The most surprising property of compound *(8)* is its thermal lability: at room temperature it is already converted into 5,7-dimethyl-*cis*-bicyclo[5.4.0]undeca-2,4,8,10-tetraene *(9)* (100%).

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In CCl_4 solution at 26 °C the transformation proceeds as a first order reaction; $k = (1.31 + 0.06) \times 10^{-5}\ s^{-1}$. Unequivocal proof of the presence of *(9)* is provided by the X-ray structure analysis (Fig. 1) of its cycloadduct *(11)* with ETAD, which is formed together (ratio 3:4) with its stereoisomer having an *endo* seven-membered ring (m.p. 112 °C) in acetone at 0 °C. In the low-pressure chromatographic separation on silica gel with hexane/ethyl acetate (4:1), *(11)* is eluted as second component (20 %) and is subsequently recrystallized from ether. The adduct *(11)* is formed by attack of the dienophile on the six-membered ring from the concave side of the bicyclic compound *(9)*. The planes of the double bonds in the seven-membered ring of the adduct form an angle of 38.5°.

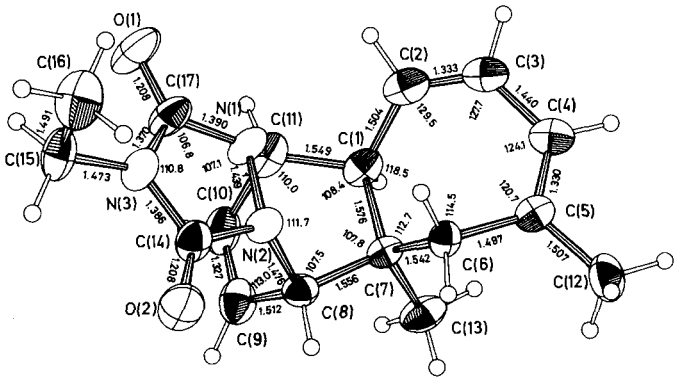
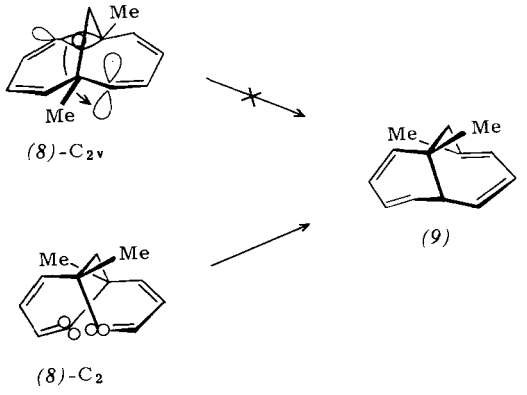


Fig. 1. Molecular structure of the cycloadduct *(11)* of 4-ethyl-1,2,4-triazolinedione (ETAD) and 5,7-dimethyl-*cis*-bicyclo[5.4.0]undeca-2,4,8,10-tetraene *(9)* (bond lengths in Å, bond angles in °). Compound *(11)* forms monoclinic crystals, space group $P2_1/c$ with $a = 13.684(3)$, $b = 7.607(2)$, $c = 16.142(4)$ Å; $\beta = 109.84(2)°$; $Z = 4$; $\rho_{calc} = 1.258$, $\rho_{exp} = 1.263\ g/cm^3$. The intensity measurements were carried out with an automatic single crystal diffractometer (CAD-4, Enraf Nonius) with MoK_α radiation ($3° \leq \theta \leq 30°$). The heavy atoms could be localized by direct methods; a Fourier difference synthesis gave the positions of the hydrogen atoms. Refinement of the atomic parameters (C, N, O anisotropic, H isotropic) with the structural factors of 1441 observed reflections ($I > 2\sigma_I$) converged at $R = 0.045$.

The rearrangement *(8)* → *(9)* can formally be described as a sigmatropic 1,5 shift[7] of a butadieno bridge; however, this type of reaction occurs only at elevated temperatures in the lower vinylogs *(2)* and *(1)* and is restricted to shifts of the methano bridge[1c, 8]. Another reaction course would therefore appear more likely: From a molecular model it is clear that besides the angularly-strained C_{2v} conformation for *(8)*, a twisted conformation with C_2 symmetry is possible in which the angular strain disappears but the butadiene π-orbitals are mutually pressed together with one terminus in a σ-like fashion.



The rearrangement of *(8)*-C_2, which should begin with the formation of the transannular bond, proceeds either with simultaneous loosening of bridgehead bond (cf. the photochemical di-π-methane rearrangement[9]) or *via* a twofold allyl-stabilized diradical. Thus the interaction of the two butadieno-bridges in *(8)* manifests itself rather as transannular σ-overlapping than as cyclic homoconjugation.

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CAS Registry numbers:
(4), 33237-03-5; *(5)*, 68388-80-7; *(6)*, 68388-81-8; *(7a)*, 68388-82-9; *(7b)*, 68388-83-0; *(8)*, 68388-84-1; *(9)*, 68388-85-2; *(10)*, 68388-86-3; *(11)*, 68388-87-4; 4-ethyl-1,2,4-triazolinedione, 40609-72-1

[1] a) *P. Bischof, R. Gleiter, E. Heilbronner*, Helv. Chim. Acta *53*, 1425 (1970), and references cited therein; b) *E. F. Ullman*, Chem. Ind. (London) *1958*, 1173; *A. T. Blomquist, Y. C. Meinwald*, J. Am. Chem. Soc. *81*, 667 (1959); *R. C. Cookson, S. S. H. Gilani, J. D. R. Stevens*, Tetrahedron Lett. *1962*, 615; c) *J. A. Berson, R. R. Boettcher, J. J. Vollmer*, J. Am. Chem. Soc. *93*, 1540 (1971).

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[3] a) *W. A. Böll*, Tetrahedron Lett. *1968*, 5531; b) *W. Klug*, Dissertation, Universität Köln 1972.

[4] *R. B. Turner, B. J. Mallon, M. Tichy, W. v. E. Doering, W. R. Roth, G. Schröder*, J. Am. Chem. Soc. *95*, 8605 (1973).

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[6] The cycloadduct obtained from ETAD and *(2)* at 0 °C in acetone solution melts at 102—104 °C.

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[8] *W. M. Halper, G. W. Gaertner, E. W. Swift, G. E. Pollard*, Ind. Eng. Chem. *50*, 1131 (1958).

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1-(1-Adamantyl)-1-methylethoxycarbonyl: A New Protecting Group for Peptide Syntheses

By *Hubert Kalbacher* and *Wolfgang Voelter*[*]

Although the well-known amino protecting groups of the urethane type (*tert*-butyl- and benzyloxycarbonyl) fullfil many requirements of straightforward peptide synthesis[1], it is often desirable to liberate NH_2 groups under very mild acidolytic conditions so that an optimal protection of acid-labile residues can be achieved in syntheses involving repetitive coupling and deblocking steps (solid phase method) and the indole system of tryptophan-containing peptides remains intact.

The protecting groups Ppoc[2a], Bpoc[2b], Ddz[3], or Azoc[4] accommodate these requirements; however, only the first two have found general use. In both cases the storage of the protected amino acids is not unproblematical[5] owing to autocatalytic decomposition and photolability. Also the Bpoc phenyl carbonate frequently used for introduction of the Bpoc group tends to decompose even at low temperatures[6]. Bpoc-Trp-OH can be synthesized in only low yields.

The new protecting group 1-(1-adamantyl)-1-methylethoxycarbonyl (Adpoc) not only has all the advantages of the above mentioned α,α-dimethylbenzyloxycarbonyl-type protecting groups but is also stable towards hydrogenolysis in peptide syntheses. Incorporation of the Adpoc group can be achieved by means of the crystalline 1-(1-adamantyl)-1-methylethyl phenyl carbonate (Adpoc-OPh) *(4)*.

The Adpoc group can be removed in mild acidolytic medium, preferably 3 % trifluoroacetic acid in dichloromethane, within 4—5 min at 0 °C or 2—3 min at room temperature. Under these conditions the Adpoc group is removed 10^3 times faster than the Boc group; consequently it is possible to use Adpoc selectively in conjunction with the Boc group,

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and naturally also benzyloxycarbonyl-, benzyl ether-, and benzyl ester-protecting groups. On the other hand, under acidolytic conditions the Adpoc amino acids are about two to three times more stable than the Bpoc amino acids. The properties of some Adpoc amino acids and peptides (commercially available from Senn Chemicals, CH-8157 Dielsdorf, Switzerland) are listed in Table 1.

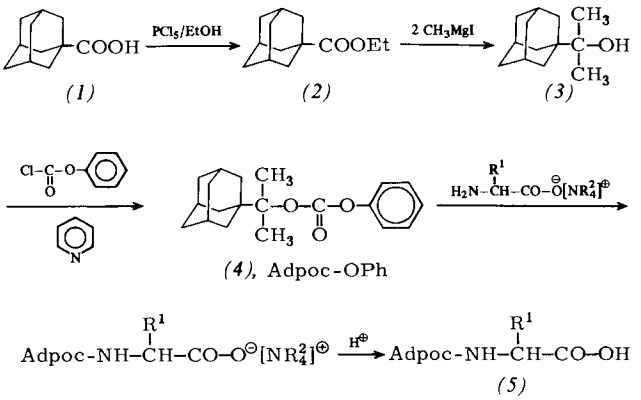


Table 1. Yields and physical data of selected Adpoc amino acids and peptides.

Compound	Yield [%]	M.p. [°C]	$[\alpha]_D^{20}$ [°]
Adpoc-L-Ala·DCHA [a]	75	155	+6.22 (c = 0.65 EtOH)
Adpoc-L-Trp-OH	72	116	−6.8 (c = 1.04 MeOH)
Adpoc-L-Trp-L-Lys(Z)-OH	73	114—116	−8.7 (c = 0.5 MeOH)
Adpoc-L-Thr(Bzl)-L-Phe-OH	67	75—76 (dec.)	−18.67 (c = 0.7, DMF)

[a] DCHA = dicyclohexylamine.

For the synthesis of Adpoc-OPh *(4)*, 1-adamantanecarboxylic acid *(1)* is converted by reaction with phosphorus pentachloride/ethanol into the ethyl ester *(2)*, which on reaction with Grignard reagent (from methyl iodide and magnesium) affords the tertiary alcohol 2-(1-adamantyl)-2-propanol *(3)*[7]. The carbonate *(4)* can be obtained by treatment of *(3)* with phenyl chloroformate.

Experimental

Synthesis of *(4)*: A solution of *(3)* (19.4 g, 0.1 mol) in dichloromethane (100 ml) is treated dropwise at −5 °C with a solution of phenyl chloroformate (15.2 ml) in dichloromethane (50 ml). The precipitate formed during the addition is redissolved on stirring the mixture overnight at 0 °C. The solution is poured onto ice, diluted with 150 ml dichloromethane and the organic phase is washed three times with water before drying over sodium sulfate. Removal of solvent by evaporation *in vacuo* at 30 °C and two recrystallizations from benzene/*n*-hexane affords long colorless crystals, m.p. 72 °C, yield 26.25 g (83.5 %).

Synthesis of *(5)*, $R^1 = CH_3$: 891 mg (10 mmol) of L-Ala-OH is dissolved with gentle warming in 4.6 ml of a *ca.* 40% solution of Triton B (benzyltrimethylammonium hydroxide) in methanol. After removal of solvent the residue is rendered free of water by azeotropic distillation with 2 × 30 ml dimethylformamide. The residue is taken up in 30 ml dimethylformamide at 50 °C and treated with 3.8 g (12 mmol) of *(4)*. After three hours' stirring at 50 °C the reaction mixture is partitioned between water and diethyl ether/petroleum ether (1:1) and the separated aqueous phase acidified at 0 °C with 1 N citric acid solution (pH = 2—3) and exhaustively extracted with diethyl ether. After the usual washing and drying the ether extracts are evaporated down *in vacuo*. The residue is taken up in a small amount of ether and finally crystallized by addition of dicyclohexylamine.

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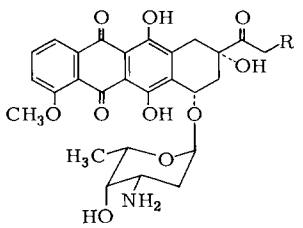
CAS Registry numbers:
(1), 828-51-3; *(2)*, 2094-73-7; *(3)*, 775-64-4; *(4)*, 68388-88-5; *(5)* (R' = CH_3), 68388-89-6; phenyl chloroformate, 1885-14-9; L-Ala-OH, 56-41-7; Adpoc-L-Ala·DCHA, 68388-90-9; Adpoc-L-Trp-OH, 68388-91-0; Adpoc-L-Trp-Lys(Z)-OH, 68388-92-1; Adpoc-L-Thr(Bzl)-Phe-OH, 68388-93-2

[1] *E. Wünsch* in Houben-Weyl-Müller: Methoden der Organischen Chemie. Vol. XV/1. Thieme, Stuttgart 1974.
[2] a) Ppoc(α,α-dimethylbenzyloxycarbonyl): *P. Sieber, B. Iselin*, Helv. Chim. Acta *51*, 614 (1968); b) Bpoc(1-*p*-biphenylyl-1-methylethoxycarbonyl): *51*, 622 (1968).
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[4] Azoc(α,α-dimethyl-4-phenylazobenzyloxycarbonyl): *A. T. Kyi, R. Schwyzer*, Helv. Chim. Acta *59*, 1642 (1976).
[5] *E. Schnabel, G. Schmidt, E. Klauke*, Justus Liebigs Ann. Chem. *743*, 69 (1971).
[6] *R. S. Feinberg, R. B. Merrifield*, Tetrahedron *28*, 5865 (1972).
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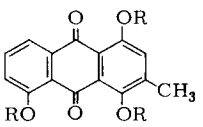
Regioselective Synthesis of the Anthraquinones Digitopurpone and Islandicin[**]

By *Manfred Braun*[*]

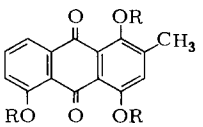
The importance attained by the anthracycline antibiotics daunomycin *(1a)* and adriamycin *(1b)* as chemotherapeutic agents against various types of cancer[1a] has recently led to an intensive search for new routes for the synthesis of such anthraquinones[1b–1e]. Astonishingly, however, the methods previously adopted for the synthesis of such simple anthraquinones as those of the isomeric digitopurpone *(2a)* (from *Digitalis purpurea*)[2a] and islandicin *(3a)* (from *Penicillium islandicum*)[2b] are mostly tedious, unproductive, and, in part, non-regioselective *i.e.* a mixture of *(2a)* and *(3a)* is obtained[3].



(1a): R = H
(1b): R = OH



(2a): R = H
(2b): R = CH_3

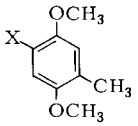


(3a): R = H
(3b): R = CH_3

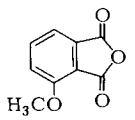
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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

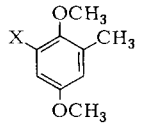
We have now tried to add aryllithium compounds such as *(4b)* to the anhydride *(5)* in such a way that only the sterically less hindered carbonyl group *meta* to the methoxy group is attacked[4]. The acid *(7a)* or its tautomer *(7a')* formed in this way could then be converted into the trimethyl ether *(2b)* by intramolecular Friedel-Crafts acylation and subsequently into digitopurpone *(2a)* by demethylation.



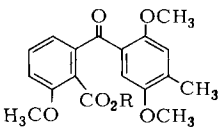
(4a): X = Br
(4b): X = Li
(4c): X = MgBr



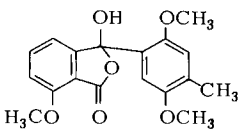
(5)



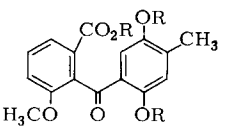
(6a): X = Br
(6b): X = MgBr



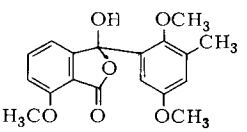
(7a): R = H
(7b): R = CH_3



(7a')



(8a): R = H
(8b): R = CH_3



(9)

Reaction of the anhydride *(5)* with a solution of *(4b)* (prepared from the bromide *(4a)*[5] and *n*-butyllithium) in hexane/tetrahydrofuran (THF)/tetramethylethylenediamine (TMEDA) did not lead to the desired result. A crude product mixture (m.p. 115—160°C, 58% yield) was formed, which on reaction with diazomethane afforded a 1:1 mixture of the thin-layer chromatographically (neutral $Al_2O_3/CHCl_3$) separable isomeric esters *(A)* ($R_F = 0.55$) and *(B)* ($R_F = 0.44$). The constitution of *(A)* as *(8b)* was proven by mixed melting point (127—128°C) and by the agreement of the IR and ^{1}H-NMR spectra with those of the ester *(8b)* prepared from authentic[3a] acid *(8a)* and diazomethane. The isomer *(B)* thus has the constitution *(7b)*.

On the other hand, reaction of the Grignard compound *(4c)* with *(5)* in THF/TMEDA and esterification of the crude product with diazomethane leads, according to the ^{1}H-NMR spectrum, to a mixture of the esters *(7b)* and *(8b)* in the ratio 97:3. Single recrystallization of the crude adduct formed from *(4c)* and *(5)* affords the isomer-free, analytically pure pseudo acid *(7a')*. This can be converted by 15 hours' stirring in conc. sulfuric acid at room temperature into *(2b)*, whose demethylation in 48% HBr/glacial acetic acid leads to digitopurpone *(2a)* in 51% overall yield. Both *(2a)* and *(2b)* are characterized by their spectroscopic data and by mixed melting points with authentic[3a] samples of *(3a)* and *(3b)*, respectively; the ^{1}H-NMR spectra of *(2a)* and *(2b)* show no traces of the isomers *(3a)* and *(3b)*.

Islandicin *(3a)* can be prepared analogously: Reaction of the Grignard compound *(6b)*, obtained from the bromide *(6a)*[6], with *(5)* in THF/TMEDA and recrystallization of the crude product from methanol/water leads to the isomer-free, analytically pure pseudo acid *(9)*[7] in 38% yield. In conc. sulfuric acid *(9)* is converted into *(3b)*, whose demethylation affords islandicin *(3a)* in 75% yield [based on *(9)*]; the spectroscopic data and the mixed melting point are identical with those of an authentic[3a] sample, and no *(2a)* is obtained.

Application of this new, regioselective anthraquinone synthesis—giving digitopurpone *(2a)* and islandicin *(3a)* in 51 and 29% overall yields, respectively—to the preparation of *(1)* and *(2)* is under investigation.

Experimental[8]

Synthesis of *(7a')*: To 10 ml THF, which is heated to boiling along with 150 mg (6.2 mmol) magnesium turnings and 5 mg iodine under N_2, are added 2 ml of a solution of *(4a)* (1.155 g, 5 mmol) in THF (8 ml), then 20 µl methyl iodide and finally the remaining solution of the bromide *(4a)*. The mixture is boiled for 90 min, cooled to room temperature, treated with 2 ml TMEDA and the resulting solution finally added within 5 min at −78°C to a stirred suspension of *(5)* (890 mg, 5 mmol) in THF (30 ml) under N_2. After one hours' stirring at −78°C the mixture is allowed to warm to room temperature within *ca.* 12 h; 5 ml H_2O is added and the solvent removed in a rotary evaporator. The residue is taken up in 100 ml ether and 200 ml 7% aqueous KOH solution. After separation of the aqueous phase and repeated extraction of the ethereal phase with 100 ml 7% KOH solution the combined KOH phases are cooled with ice, brought to pH = 1 with conc. hydrochloric acid, and extracted with a total of 300 ml $CHCl_3$. Washing of the combined $CHCl_3$ phases with saturated NaCl solution, drying over Na_2SO_4, and removal of the solvent *in vacuo* affords 1.12 g of an oil, which freezes on addition of $CHCl_3$/pentane. Recrystallization from CH_3OH/H_2O yields 1.04 g (63%) *(7a)*, m.p. 183—185°C; IR (KBr): 3350 (OH), 1735 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 4.02$ (s), 3.89 (s), 3.57 (s) (each 3H, OCH_3); 2.21 (s, 3H, aryl-CH_3). *(9)* is synthesized analogously: m.p. 175—176°C (CH_3OH/H_2O); IR (KBr): 3370 (OH), 1745 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 4.03$ (s), 3.98 (s), 3.62 (s) (each 3H, OCH_3); 2.34 (s, 3H, aryl-CH_3).—Ester *(7b)*: b.p. 120°C (bath)/0.002 torr; IR ($CHCl_3$): 1725 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 3.90$ (s), 3.79 (s), 3.75 (s), 3.60 (s) (each 3H, OCH_3); 2.27 (s, 3H, aryl-CH_3).—Ester *(8b)*: m.p. 128—129°C; IR (KBr): 1720 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 3.87$ (s), 3.72 (s), 3.70 (s), 3.39 (s) (each 3H, OCH_3); 2.24 (s, 3H, aryl-CH_3).

Synthesis of *(2b)*: A solution of *(7a')* (78 mg, 0.24 mmol) in conc. sulfuric acid (10 ml) is stirred for 15 h at room temperature, diluted with 200 ml ice-water, and extracted with $CHCl_3$. After drying over Na_2SO_4 and removal of the solvent there remain 74 mg (100%) *(2b)*, m.p. 161°C (163°C after recrystallization from ethanol, Ref. [3b] 163—164°C).

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CAS Registry numbers:
(2a), 34425-57-5; *(2b)*, 51837-73-1; *(3a)*, 476-56-2; *(3b)*, 50457-06-2; *(4a)*, 13321-74-9; *(4b)*, 68409-17-6; *(5)*, 14963-96-3; *(6a)*, 13523-12-1; *(7a)*, 68409-18-7; *(7a')*, 68409-19-8; *(7b)*, 68409-20-1; *(8b)*, 68409-21-2; *(9)*, 68409-22-3

[1] a) *D. W. Henry* in: Cancer Chemotherapy. ACS Symp. Ser. *30*, 15 (1976), and references cited therein; b) *A. S. Kende et al.*, J. Am. Chem. Soc. *97*, 4425 (1975); *98*, 1967 (1976); Tetrahedron Lett. *1977*, 3537; c) *T. R. Kelly et al.*, *ibid. 1976*, 3869, 3873; d) *C. J. Sih et al.*, *ibid. 1976*, 3385; *1977*, 2303; J. Am. Chem. Soc. *100*, 2272 (1978); e) *J. S. Swenton et al.*, Tetrahedron Lett. *1977*, 2383.

[2] a) *E. J. C. Brew, R. H. Thomson*, J. Chem. Soc. *C 1971*, 2007; b) *B. H. Howard, H. Raistrick*, Biochem. J. *44*, 227 (1949).

[3] a) *S. Neelakantan, T. R. Rajagopalan, T. R. Seshadri*, Proc. Indian Acad. Sci. *49A*, 234 (1959); Chem. Abstr. *54*, 1465f (1960); b) *A. S. Kende et al.*, Synth. Commun. *3*, 387 (1973); c) *A. S. Kende et al.*, Tetrahedron Lett. *1973*, 2935; d) *C. J. Sih et al.*, J. Chem. Soc. Chem. Commun. *1978*, 242; e) *M. E. Jung et al.*, J. Org. Chem. *42*, 2371 (1977).

[4] Cf. *M. S. Newman, P. G. Scheurer*, J. Am. Chem. Soc. *78*, 5004 (1956). Reaction of phthalic anhydride with phenyllithium: *W. E. Parham, R. M. Piccirilli*, J. Org. Chem. *41*, 1268 (1976).
[5] *A. Lüttringhaus, H. Gralheer*, Justus Liebigs Ann. Chem. *550*, 67 (1942).
[6] *H. Raistrick, R. Robinson, D. E. White*, Biochem. J. *30*, 1303 (1936).
[7] According to the ^{1}H-NMR spectrum, formation of up to a maximum of 5% of the isomer—by addition of *(6b)* to the sterically more hindered carbonyl group of *(5)*—cannot be ruled out.
[8] Correct analytical values were obtained for the new compounds.

The Synthesis of Unsymmetrical Tetraarylporphyrins on Solid Phases[**]

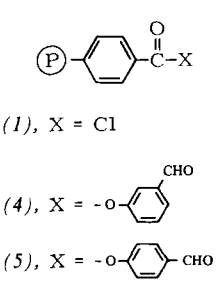
By *Clifford C. Leznoff* and *Polina I. Svirskaya*[*]

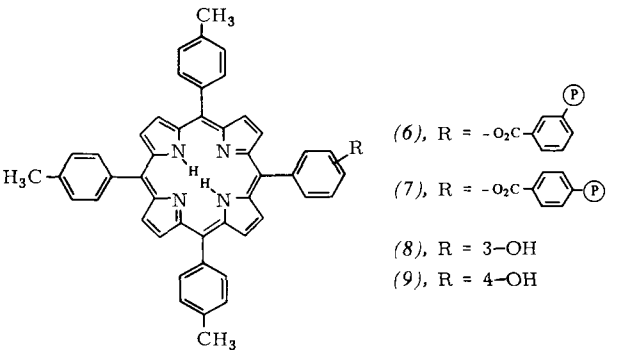
There has been tremendous interest recently directed toward the synthesis of model porphyrin systems related to the oxygen-binding proteins[1]. In addition, the synthesis of model dimers and higher aggregates of porphyrins are of particular interest in studies of the photo-oxidation of water to oxygen during photosynthesis[2]. The *symmetrical* tetraarylporphyrins had long been widely used as models in both of these systems due to their ease of preparation[3], but some more recent sophisticated work required the synthesis of *unsymmetrical* tetraarylporphyrins, which were synthesized in yields ranging from 0.5—5%[4]. Furthermore, the desired product could only be isolated from the many other compounds produced by extensive chromatographic separations.

Although preformed hemes and porphyrin models have been attached to insoluble supports[5] and unusual synthetic polymers incorporating the heme function have been described[6], the actual synthesis of a porphyrin on polymer supports from its simple precursors has not been described. Insoluble polymer supports provide a suitable means of "fishing out" a minor component from a complex reaction mixture[7a] and we have utilized these supports in this way to prepare monoblocked derivatives of a wide variety of symmetrical difunctional compounds[7b].

We now report that insoluble polymer supports can be used to prepare unsymmetrical tetraarylporphyrins and aid in their isolation. Thus a 2% crosslinked divinylbenzene-styrene copolymer *(1)* containing 1.7 mmol of benzoyl chloride functional groups per g polymer[8], was treated with 3-hydroxybenzaldehyde *(2)* or 4-hydroxybenzaldehyde *(3)* to give the polymer-bound benzoylbenzaldehydes *(4)* and *(5)*, respectively. Cleavage of *(4)* and *(5)* with 0.5 M sodium hydroxide/dioxane (1:1) at room temperature for 20 h liberated 0.73 mmol of *(2)* and 1.06 mmol of *(3)*/g of *(4)* and *(5)*, respectively. Treatment of *(4)* and *(5)* with *p*-tolualdehyde and pyrrole in hot propionic acid for 1 h yielded upon filtration black polymers which were readily washed free of tetratolylporphyrin by extraction in a Soxhlet extractor with chloroform for 2 h to yield the polymer-bound unsymmetrical tetraarylporphyrins *(6)* and *(7)*, respectively. Cleavage of *(6)* and *(7)* with potassium carbonate in methanol for 24 h yielded black powders *essentially free of tetratolylporphyrin* present in large amounts in a comparable solution synthesis[4a].

The black powders can be readily purified by a quick filtration through a silica column using chloroform as eluant followed by preparative thin-layer chromatography using benzene/ether/chloroform (7:2:1) as eluant to give 5-(3-hydroxyphenyl)-10,15,20-tritolylporphyrin *(8)* in 2% yield and 5-(4-hydroxyphenyl)-10,15,20-tritolylporphyrin *(9)* in 4.5% yield,





both as purple crystals. The NMR spectra of *(8)* and *(9)* were identical with the published spectra[4a] and the mass spectra exhibited peaks of 672 (M^+) and 336 (M^{2+}) typical of tetraarylporphyrins[9].

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CAS Registry numbers:
(2), 100-83-4; *(3)*, 123-08-0; *(8)*, 57412-06-3; *(9)*, 57412-08-5; *p*-tolualdehyde, 104-87-0; pyrrole, 109-97-7

[1] See, *e.g. J. W. Buchler*, Angew. Chem. *90*, 425 (1978); Angew. Chem. Int. Ed. Engl. *17*, 407 (1978), and references cited therein; *J. P. Collman*, Acc. Chem. Res. *10*, 265 (1977), and references cited therein.
[2] *J. H. Fuhrhop*, Angew. Chem. *88*, 704 (1976); Angew. Chem. Int. Ed. Engl. *15*, 648 (1976); *F. P. Schwarz, M. Goutterman, Z. Muljiani, D. H. Dolphin*, Bioorg. Chem. *2*, 1 (1972).
[3] *A. D. Adler, F. Longo, J. Finarelli, J. Goldmacher, J. Assour, L. Korsakoff*, J. Org. Chem. *32*, 476 (1967).
[4] a) *R. G. Little, J. A. Anton, P. A. Loach, J. A. Ibers*, J. Heterocycl. Chem. *12*, 343 (1975); b) *J. A. Anton, J. Kwong, P. A. Loach, ibid. 13*, 717 (1976); c) *J. P. Collman, C. M. Elliot, T. R. Halbert, B. S. Tourog*, Proc. Nat. Acad. Sci. USA *74*, 18 (1977).
[5] *O. Leal, D. L. Anderson, R. G. Bowman, F. Basolo, R. L. Burwell, Jr.*, J. Am. Chem. Soc. *97*, 5125 (1975); *E. Tsuchida, K. Honda, H. Sata*, Inorg. Chem. *15*, 352 (1976).
[6] *E. Bayer, G. Holzbach*, Angew. Chem. *89*, 120 (1977); Angew. Chem. Int. Ed. Engl. *16*, 117 (1977).
[7] a) *I. T. Harrison, S. Harrison*, J. Am. Chem. Soc. *89*, 5723 (1967); *C. C. Leznoff, J. Y. Wong*, Can. J. Chem. *50*, 2892 (1972); *J. M. J. Fréchet, L. J. Nuyens, ibid. 54*, 926 (1976); *J. Y. Wong, C. Manning, C. C. Leznoff*, Angew. Chem. *86*, 743 (1974); Angew. Chem. Int. Ed. Engl. *13*, 666 (1974); b) *C. C. Leznoff*, Acc. Chem. Res. *11*, 327 (1978).
[8] *T. M. Fyles, C. C. Leznoff*, Can. J. Chem. *54*, 935 (1976); *M. J. Farrall, J. M. J. Fréchet*, J. Org. Chem. *41*, 3877 (1976); *T. M. Fyles, C. C. Leznoff, J. Weatherston*, Can. J. Chem. *54*, 1031 (1978).
[9] *M. Meot-Ner, J. H. Green, A. D. Adler*, Ann. N. Y. Acad. Sci. 206, 641 (1973).

Addition of Water to *o*-Phenylethynyl-Substituted Triphenylphosphanes

By *Werner Winter*[*]

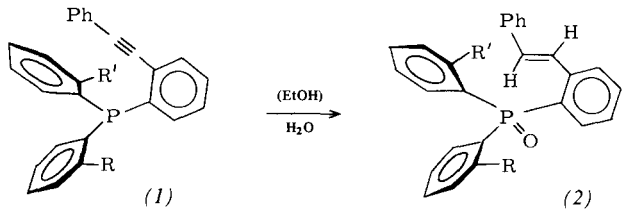
Surprisingly, on recrystallization of the *o*-phenylethynyl-substituted triphenylphosphane *(1a)*[1a] from commercial ethanol, the triphenylphosphane oxide *(2a)* containing a stereo-

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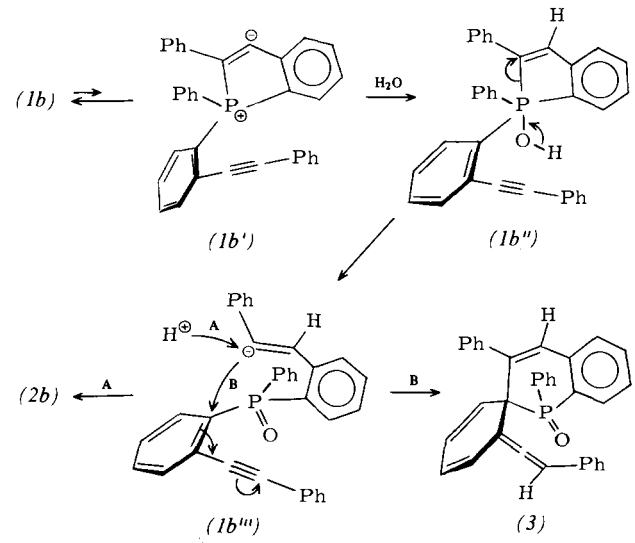
specifically formed *trans*-stilbene structural unit could be isolated. The analogous reaction with phosphanes *(1b)* and *(1c)*[1b] likewise led stereospecifically to the phosphane oxides *(2b)* and *(2c)*, respectively. The products *(2a)*—*(2c)* formed by formal addition of H_2O could be characterized on the basis of their spectroscopic data[2].



(a), R, R' = H; *(b)*, R = —≡—Ph, R' = H; *(c)*, R, R' = —≡—Ph

Compounds *(1a)*—*(1c)* remained completely stable in hot anhydrous ethanol and could be recrystallized "normally". Hence, the added H_2O must have originated from the commercial ethanol. The reaction was found to take place also in other water-containing solvents, *e.g.* acetone/H_2O. On using aprotic solvents (*e.g.* acetone) and D_2O the deuterated *trans*-olefins were formed.

The course of the reaction is discussed in more detail for bis(phenylethynyl)phosphane *(1b)*, since in this case a further product *(3)* could be isolated which affords additional information on the mechanism of the reaction.



Intramolecular nucleophilic attack of the phosphorus at a sterically favorable acetylene C-atom[3] in *(1b)* leads to the intermediate *(1b')*, which can be stabilized in the presence of H_2O as the hydroxyphosphorane *(1b'')*. *(1b'')* decomposes with cleavage of the apical P—C_{olefin} bond to the intermediate *(1b''')*, which on protonation of the carbanionic olefin C-atom affords the stable end-product *(2b)* (route A). However, the carbanionic olefin C-atom can also attack a benzene ring nucleophilically leading to formation of the compound *(3)* containing a spiro-cyclohexadiene-allene structural unit (route B). In the presence of HCl only *(2b)* is formed: apparently the protonation of the carbanion C-atom proceeds more rapidly than that of the nucleophilic addition to the benzene ring. The unusual structure of *(3)* was confirmed by X-ray structure analysis[4].

The reaction *(1)* → *(2)* appears remarkable on two counts: On simple "recrystallization", the *o*-phenylethynyl-substituted triphenylphosphanes *(1a)*—*(1c)* can be transformed stereospecifically into triphenylphosphane oxides with *trans*-stilbene and tolan structural units. Reduction of these phosphane oxides *(2)* with $SiHCl_3$[5] leads to formation of novel transition metal ligands with phosphane, acetylene, and olefin donor sites within *one* molecule. Furthermore, the reaction route B represents on of the few examples[6] in which a phenyl substituent is attacked nucleophilically by the leaving group after apical ring-opening of a cyclic hydroxyphosphorane.

Exclusive attack of the phenylethynyl-substituted phenyl ring in *(1b'')* might therefore be explained by formation of a cyclohexadiene-allene system capable of conjugation.

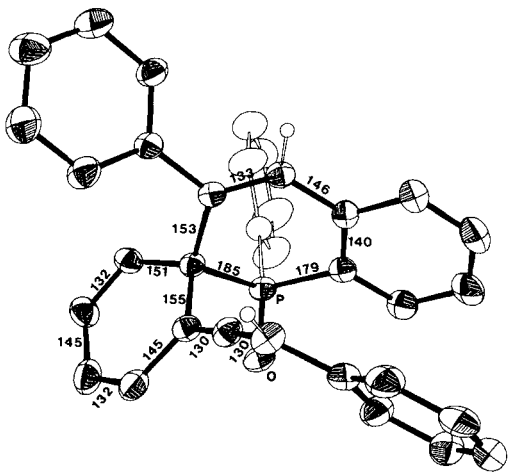


Fig. 1. Molecular structure of *(3)*. For sake of clarity only the "added" H atoms are shown. The standard deviations of the bond lengths (in pm) are on average 0.5 pm [4].

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CAS Registry numbers:
(1a), 58581-32-1; *(1b)*, 54100-67-3; *(1c)*, 68457-25-0; *(2a)*, 68457-26-1; *(2b)*, 68457-27-2; *(2c)*, 68457-28-3; *(3)*, 68457-29-4; H_2O, 7732-18-5

[1] a) *W. Winter*, Angew. Chem. *88*, 260 (1976); Angew. Chem. Int. Ed. Engl. *15*, 241 (1976); b) synthesis of *(1b)*: *W. Winter*, Chem. Ber. *109*, 2405 (1976); synthesis of *(1c)*: analogous to *(1b)*.

[2] *(2a)*: yield 76 %, colorless crystals, m.p. 169—170 °C (cyclohexane/benzene); IR: 1195 (P=O) and 960 cm^{-1} (C—H out-of-plane for *trans*-olefin); ^{1}H-NMR (TMS, $CDCl_3$): olefin AB-system: $\delta_A = 7.83$, $\delta_B = 6.87$, $J_{AB} = 16$ Hz; *(2b)*: yield 54 %, colorless crystals, m.p. 160—161 °C (EtOH); IR: 2225 (—C≡C—), 1190 (P=O) and 965 cm^{-1} (*trans* olefin); ^{1}H-NMR (TMS, $CDCl_3$): olefin AB-system: $\delta_A = 7.80$, $\delta_B = 6.83$, $J_{AB} = 16$ Hz; *(2c)*: yield 88 %, colorless crystals, m.p. 205—207 °C (EtOH); IR: 2210 (—C≡C—), 1190 (P=O) and 950 cm^{-1} (*trans*-olefin; ^{1}H-NMR (TMS, $CDCl_3$): olefin AB-system: $\delta_A = 7.62$, $\delta_B = 6.38 = 16$ Hz.

[3] *D. W. Allen, J. C. Tebby*, Tetrahedron *23*, 2795 (1967).

[4] Monoclinic, space group $P2_1/c$; $a = 873.7(2)$, $b = 1817.4(10)$, 1639.8(5) pm, $\beta = 104.16(2)°$; $Z = 4$; 2413 symmetry independent reflections [$I \geq 2\sigma(I)$], Nonius CAD-4, MoK_α-graphite monochromator; determination of phases by direct methods (SHELX); refinement: $R = 0.042$ (P, O, C anisotropically, H isotropically).

[5] *W. Winter*, unpublished results.

[6] *S. E. Fishwick, J. Flint, W. Hawes, S. Tripett*, Chem. Commun. *1967*, 1113; *S. E. Cremer, ibid. 1968*, 1132; *D. Hellwinkel, H.-J. Wilfinger*, Chem. Ber. *105*, 3878 (1972).

Enantiomerism and Diastereoisomerism of Bishelical Bilatriene Dimers in the Crystal Lattice

By *Harald Lehner, Silvia E. Braslavsky*, and *Kurt Schaffner*[*]

The *all-Z-all-syn* stereoisomers of bilatrienes are helical in the crystal lattice[1, 2]. In addition, appropriately structured

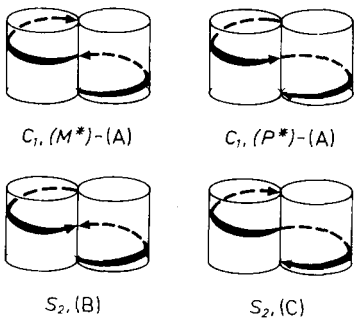
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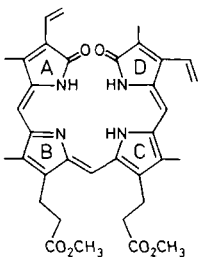
[++] To whom correspondence should be addressed.

molecules form bishelical dimers, by way of intermolecular N—H···O bridges. If a helical bilatriene monomer possesses C_2 symmetry, *i.e.*, if the substitution patterns of rings *A* and *D* and of rings *B* and *C* are identical, dimerization can lead to *one* such bishelical arrangement only; it has a center of inversion and consequently it is achiral.

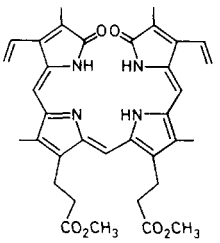
Structural data[1,3] of the unsymmetrically substituted biliverdin dimethyl ester *(1)* reveal positional disorders of the substituents which have not been satisfactorily explained as yet. The single helices have no symmetry element in this case (C_1). Instead, they are characterized by an orientation as defined, *e.g.*, by the sequence of rings $A \rightarrow D$, which for the dimerization to bishelices now offers *four* possible combinations, *(M*)*-(A), *(P*)*-(A), (B), and (C).



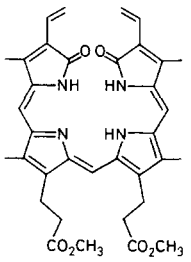
(B) and (C) are achiral, and they are diastereoisomeric with respect to each other and to the enantiomers *(M*)*-(A) and *(P*)*-(A)[5]. If the substituents do not strongly perturb the C_2 symmetry of the bilatriene skeleton, the three bishelical aggregates (A), (B), and (C) will differ only slightly in energy, and they can be expected therefore to coexist with comparable probabilities in the crystal lattice. It is now evident that, whenever more than one of these three bishelical arrangements occur simultaneously, positional disorders of the substituents will be simulated and thus impede the interpretation of X-ray data.



(1)



(2)



(3)

Biliverdin dimethyl ester *(1)*, with the substitution pattern unsymmetrical only with respect to the methyl and vinyl positions at rings *A* and *D*, fulfils the requirements for testing the relevance of our model considerations. A recent X-ray analysis[1] does in fact show a considerable disorder for the ring *A* and *D* substituents. However, the homogeneity of the crystal used had not been ascertained conclusively[6]. A single crystal X-ray analysis[3] of pure *(1)*[4] has now revealed a qualitatively similar disorder[1].

The result could also arise from a crystal composed of a 1:1 complex of *(2)* and *(3)*. This possibility was unequivocally ruled out in an isotope dilution experiment. Equal amounts of $[D_6]$-*(1)*[7] and *(2)* were dissolved in boiling chloroform and then separated again by chromatography[4]. The two products were indistinguishable from the corresponding starting materials by 270 MHz ^{1}H-NMR and mass spectra, thus confirming the isomeric homogeneity of our X-ray sample.

The X-ray analytical disorder of the substituents of *(1)* can thus be rationalized in terms of head-to-head, head-to-tail, and tail-to-tail dimerizations of the single helices occurring with comparable probabilities, *i.e.* by the presence of several diastereoisomeric and/or enantiomeric bishelical bilatriene dimers. A similar situation has possibly been encountered in the case of bilirubin with ridge-tile conformation[8].

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CAS Registry numbers:
(1), 26615-10-1; *(2)*, 26458-42-4; *(3)*, 26458-43-5

[1] *W. S. Sheldrick*, J. Chem. Soc., Perkin Trans. II *1976*, 1457.

[2] *J. V. Bonfiglio, R. Bonnett, M. B. Hursthouse, K. M. A. Malik, S. C. Naithani*, J. Chem. Soc. Chem. Commun. *1977*, 829; *G. Struckmeier, J. Engel, ibid. 1978*, 33; *W. S. Sheldrick, A. Borkenstein, J. Engel, G. Struckmeier*, J. Chem. Res. (M) *1978*, 1616, and references cited therein; *G. Struckmeier, U. Thewalt, J.-H. Fuhrhop*, J. Am. Chem. Soc. *98*, 278 (1976); *J. V. Bonfiglio, R. Bonnett, M. B. Hursthouse, K. M. A. Malik*, J. Chem. Soc. Chem. Commun. *1977*, 83.

[3] Unpublished results by *S. Mohr, Y.-H. Tsay, C. Krüger*, whom we thank for helpful discussions and for communicating their crystal data of biliverdin dimethyl ester *(1)* [4]: space group $P\bar{1}$, $a = 12.419(4)$, $b = 14.609(5)$, $c = 9.790(2)$ Å, $\alpha = 111.82(2)$, $\beta = 90.69(2)$, $\gamma = 97.38(2)°$, $V = 1631.8$ Å^3, $Z = 2$. $R = 0.1180$ for 1938 observed reflections, $I \geq 2.0\sigma(I)$. Disorder as in [1]. Refinement of two independent molecules in P1 ($R = 0.0880$) did not substantially change the disorder model.

[4] *S. E. Braslavsky, A. R. Holzwarth, H. Lehner, K. Schaffner*, Helv. Chim. Acta *61*, 2219 (1978); *H. Lehner, S. E. Braslavsky, K. Schaffner*, Justus Liebigs Ann. Chem. (1978), in press.

[5] The stereochemical relationship of these four bishelices is similar to the cyclostereoisomerism of catenanes, with *(M*)*-(A) and *(P*)*-(A) corresponding to cycloenantiomers and (B) and (C) to cyclodiastereoisomers; see *R. Cruse* in *E. L. Eliel*: "Stereochemie der Kohlenstoffverbindungen", Verlag Chemie, Weinheim 1966, pp. 215–225; *H. L. Frisch, E. Wasserman*, J. Am. Chem. Soc. *83*, 3789 (1961).

[6] We thank Dr. *W. S. Sheldrick* for information on the preparation and isolation procedure used for the X-ray sample (*P. Krüger*, Ph. D. Thesis, Technische Universität, Braunschweig, 1976).

[7] Compound $[D_6]$-*(1)* was obtained upon esterification of a mixture of biliverdin isomers with CD_3OD/D_2SO_4 and subsequent chromatographic separation of the esters [4]; m.p. 204—206 °C; hexadeuteration >95% by 270 MHz ^{1}H-NMR and MS.

[8] *R. Bonnett, J. E. Davies, M. B. Hursthouse*, Nature *262*, 326 (1976); *R. Bonnett, J. E. Davies, M. B. Hursthouse, G. M. Sheldrick*, Proc. R. Soc. London *B202*, 249 (1978).

Dipotassium Hexaisobutyldialuminate, a Complex Containing an Al—Al Bond

By *Heinz Hoberg* and *Siegfried Krause*[*]

The dehalogenation of diisobutylaluminum halides with alkali metals can lead, under certain conditions, to the formation of tetraisobutyldialuminum[1].

This observation encouraged us to investigate the possibility of isolating intermediates in the previously reported reaction

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(a)[2] which, at 100 °C, leads to separation of Al and formation of tetraalkylaluminate complexes.

$$4\,R_3Al + 3\,M \rightarrow 3\,M[R_4Al] + Al \qquad (a)$$
R = alkyl; aryl; M = alkali metal

When triisobutylaluminum is allowed to react with potassium in a non-polar solvent at 20 °C the separation of aluminum is completely suppressed, and we were able to isolate the novel dipotassium hexaisobutyldialuminate *(1)* containing an Al—Al bond in 63 % yield.

$$2(i\text{-}C_4H_9)_3Al + 2\,K \rightarrow K_2[(i\text{-}C_4H_9)_3Al{-}Al(i\text{-}C_4H_9)_3] \qquad (b)$$
(1)

The brown, crystalline compound *(1)*[3] (m. p. 40 °C) is readily soluble in organic solvents (toluene, diethyl ether, tetrahydrofuran) and is diamagnetic both in the crystalline state and in the solvated state. The molecular mass of 483 determined vaporimetrically in benzene (calc. 475) confirms the reported empirical formula. Solvolysis with *n*-$C_4H_9CH(C_2H_5)CH_2OD$ affords *i*-C_4H_9D and D_2 in the molar ratio 5.94 : 1 (calc. 6 : 1). In solution ionic dissociation takes place; this follows from comparison of the specific conductivity ($\varkappa = 2.87 \times 10^{-3}\ \Omega^{-1}\ cm^{-1}$; 0.2 M solution, THF, 20 °C) with that of complexes such as $K[(i\text{-}C_4H_9)_4Al]$ ($\varkappa = 4.0 \times 10^{-3}\ \Omega^{-1}\ cm^{-1}$).

The ^1H- and ^{13}C-NMR spectra of *(1)* reveal magnetic equivalence of the six *i*-C_4H_9 groups at 20 °C. No signal splitting is observed on lowering the temperature to −70 °C ([D_8]toluene), thus ruling out bridging association[4]. The upfield shift of the α-protons upon complex formation is of the expected order (Table 1).

Table 1. ^1H- and ^{13}C-NMR signals of *i*-C_4H_9—Al compounds in [D_6]benzene at 20 °C (R = *i*-C_4H_9).

	R_3Al	$K[R_4Al]$	$K_2[R_3Al{-}AlR_3]$ *(1)*
$\delta(^1H)(Al{-}CH_2)$	0.28 (d)	−0.25 (d)	−0.30 (d)
$\delta(^{13}C)(Al{-}C)$	25.3 (s)	26.4 (br.)	27.2 (s)

(1) behaves ambifunctionally towards electrophiles. On reaction with trimethylchlorosilane in THF the Al—Al bond remains intact; the product *(2)* can be regarded as a bistetrahydrofuran adduct of tetraisobutyldialuminum. On the other hand *(1)* reacts like alkali metal aromatic complexes[5] with allyl bromide to give 1,5-hexadiene *(3)* and $(i\text{-}C_4H_9)_3Al$.

$$(1) + 2(CH_3)_3SiCl + THF \rightarrow \underset{\displaystyle THF}{\overset{\displaystyle THF}{R_2Al{-}AlR_2}} + 2\,KCl + 2(CH_3)_3SiR$$
(2), 80 %

$$(1) + 2\,CH_2{=}CH{-}CH_2Br \rightarrow$$

$$CH_2{=}CH{-}CH_2{-}CH_2{-}CH{=}CH_2 + 2\,KBr + 2\,R_3Al$$
(6), 55 %

R = *i*-C_4H_9

Hydrocarbons with an affinity for electrons (naphthalene, anthracene, biphenyl, and cyclooctatetraene) accept electrons from *(1)* with formation of radical anions and dianions, and liberation of $(i\text{-}C_4H_9)_3Al$.

It can be concluded from the spectra and the chemical and physical behavior of *(1)* that there is a σ-bonding interaction between the two Al atoms.

Experimental

Triisobutylaluminum (83.7 g, 104.7 ml) is added dropwise at −30 °C to a vigorously stirred mixture of potassium (16.5 g, 422.0 mmol; pellets, ϕ *ca.* 1 mm) in hexane (900 ml) at a rate slow enough to prevent caking of the potassium pellets (*ca.* 8 h). The mixture is then warmed to room temperature, whereupon the potassium gradually dissolves and a viscous brown-colored product is obtained. After *ca.* 3 weeks the supernatant is removed and the residue taken up in *ca.* 300 ml toluene and filtered to remove any unreacted potassium. The filtrate is cooled to −78 °C. The crystalline product is recovered on a cold frit and dried at 10^{-3} torr. Yield 65.6 g (133.0 mmol, 63 %) *(1)*·0.2 toluene.

IR (KBr): no Al—H stretching vibrations at about 1800 cm^{-1}[6]. ^1H-NMR (Bruker WP 80 FT; [D_6]benzene, 80 MHz, TMS): δ = 7.10 (d, 0.5 H, C_6H_5), 2.17 + 2.12 (m, 1.3 H, $C_6H_5{-}CH_3$, CH), 1.3 (d, 6.0 H, CH_3), −0.3 (d, 1.9 H, CH_2); ^{13}C-NMR (Varian-XL-100-15; [D_6]benzene, 25.2 MHz, ext. TMS): δ = 27.2 (C—Al), 28.65 (CH), 29.82 (CH_3).

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CAS Registry numbers:
(1), 68457-39-6; *(2)*, 68457-38-5; *(3)*, 592-42-7; R_3Al, 100-99-2; $K[R_4Al]$, 68457-37-4; $(CH_3)_3SiCl$, 75-77-4; $CH_2{=}CH{-}CH_2Br$, 106-95-6; ^{13}C, 14762-74-4

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2,2′-Bipyridine(tetramethylcyclobutadiene)nickel(0)

By *Udo Griebsch* and *Heinz Hoberg*[*]

Nickel(0) is equally suitable both for the complexation and the synthesis of cyclic alkenes[1]. Cyclobutadienes were first stabilized by coordination to Ni(II)[2]; and only recently has the synthesis of bis(tetraphenylcyclobutadiene)nickel(0) been reported[3]. We have now been able to prepare 2,2′-bipyridine(tetramethylcyclobutadiene)nickel(0) *(2)* as an example of the previously unknown monocyclobutadienenickel(0) complexes, which are of interest in nickel-catalyzed cyclooctatetraene synthesis[4].

Reaction of tetramethylcyclobutadienenickel dichloride *(1)*[2] with sodium in the presence of bpy affords *(2)* in 63 % yield.

$$[\{(CH_3)_4C_4\}NiCl_2]_2 + 4\,Na \xrightarrow{+\,bpy}$$
(1)

$$2[(CH_3)_4C_4]Ni(bpy) + 4\,NaCl$$
(2)

(2) crystallizes in the form of lustrous copper-colored platelets and dissolves in organic solvents such as ether, tetrahydrofuran, or benzene giving intense blue solutions. The complex

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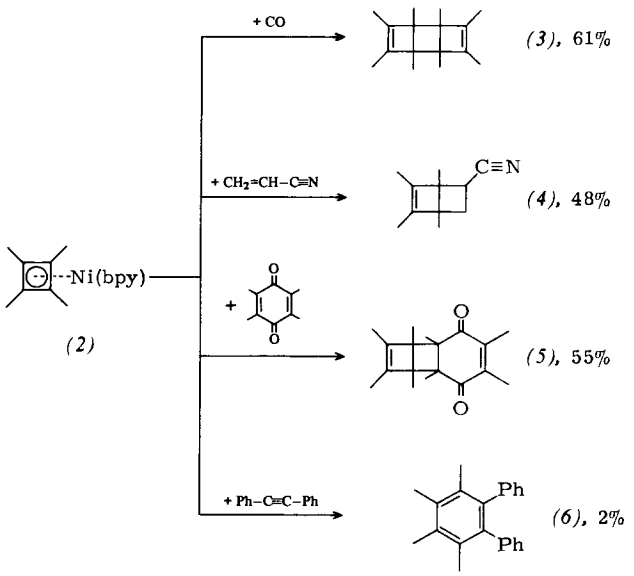
(2) is diamagnetic, exceptionally thermally stable, melts at 225°C (decomp.), and can be sublimed at 130°C/10^{-3} torr. The mass spectrum shows the molecular ion $m/e=322$ and a characteristic fragment $m/e=214$ (bpy-Ni). The relative molecular mass of 330 (calc. 323) determined cryoscopically in benzene establishes the monomeric structure.

The IR spectrum (KBr) contains the aromatic bands of bpy together with characteristic bands at 1515 (s, C=C) and 1370 and at 1435 (C—CH_3) cm^{-1}. The ^{1}H-NMR spectrum ([D_6]benzene) shows in addition to the signals of the bpy protons only one signal ($\delta=1.53$) for the 12 methyl protons of the $(CH_3)_4C_4$ system. This indicates η^4-coordination of the C_4-ring to the nickel atom. In the ^{13}C-NMR spectrum ([D_6]benzene) only two signals are observed for the C-atoms in the $(CH_3)_4C_4$ moiety. Gated-decoupled, the signal at $\delta=82.23$ could be assigned to the ring C-atoms and that at $\delta=8.48$ to the methyl C-atoms[5].

The cyclobutadiene moiety in *(2)* can be hydrogenated only with difficulty. Even after addition of catalysts such as bis(1,5-cyclooctadiene)nickel, Raney nickel, PtO_2 or Pt/C, no hydrogen is taken up in THF at 65°C (24 h, 1 atm). Only lithium in liquid ammonia effects partial hydrogenation; hydrolysis of the product affords tetramethylcyclobutene.

Tetramethylcyclobutadiene is not displaced from *(2)* by ligands (L) such as 2,2'-bipyridine or triphenylphosphane [*(2)*: L = 1:5] at 20°C in THF (8 days). However, reaction with CO (20°C, 1 atm THF) produces the dimer *(3)* (see Scheme 1).

The tetramethylcyclobutadiene system of *(2)* reacts with dienophiles (acrylonitrile, duroquinone, tolan) even at 20°C in THF (3 h) to give the Diels-Alder adducts [*(4)*, *(5)*] or their valence isomers [*(6)* (see Scheme 1).



Scheme 1. The structures of the products *(3)*—*(6)* were determined spectroscopically (MS, IR, ^{1}H-NMR), the yields by GC. *(3)* is present in the *syn*-form. There are two isomers of *(4)* (94%, 6%); presumably the *exo* isomer is the main product. *(5)* forms only one isomer (GC).

Experimental

To a vigorously stirred suspension of 7.75 g (32.6 mmol) *(1)*[2] and 5.07 g (32.5 mmol) 2,2'-bipyridine in 700 ml diethyl ether at room temperature is added 1.5 g (65 mmol) sodium (pellets, ϕ *ca.* 1 mm). The solution immediately turns blue. After *ca.* 24 h the precipitate is filtered off and washed with diethyl ether. The combined filtrates are evaporated down and dried in a high vacuum. The residue is almost analytically pure *(2)* [yield 6.55 g (20.5 mmol, 63%)]. *(2)* can be recrystallized from toluene/hexane (1:1).

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CAS Registry numbers:
(1), 33112-02-6; *(2)*, 68457-36-3; *(3)*, 1448-74-4; *(4) exo*, 67999-81-9; *(4) endo*, 67957-61-3; *(5)*, 68457-24-9; *(6)*, 21876-15-3; CH_2=CH—CN, 107-13-1; Ph—C≡C—Ph, 501-65-5

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[5] We thank Dr. *R. Mynott* for recording the ^{13}C-NMR spectra (25.2 MHz, Varian-XL-100A-15).

Redox Properties of Zinc Tetrabenzporphyrin[**]

By *Arnd Vogler, Birgit Rethwisch, Horst Kunkely, Jürgen Hüttermann*, and *Jürgen Otto Besenhard*[*]

Electron transfer processes involving metalloporphyrins play an important role in photosynthesis and other biological redox reactions. So far, the redox potentials of porphyrins could essentially only be modified by variation of the central metal and additional axial ligands[1]. A third possibility lies in the modification of the porphyrin ring. Whereas simple substituents have only a slight effect on the redox properties, an extension of the π-electron system of porphyrins could lead to a drastic decrease of the redox potentials[1]. We have found that this is indeed the case with tetrabenzporphyrin (TBP). We now report the redox behavior of zinc tetrabenzporphyrin, ZnTBP *(1)*[2], which contains a redox-inert metal center.

The results of cyclic voltammetry are explained with the aid of the reaction scheme:

$$[Zn(TBP^-)]^{\ominus} \underset{+e}{\overset{-e}{\rightleftharpoons}} [Zn(TBP)] \underset{+e}{\overset{-e}{\rightleftharpoons}}$$
(4) *(1)*

$$[Zn(TBP^+)]^{\oplus} \underset{+e}{\overset{-e}{\rightleftharpoons}} [Zn(TBP^{2+})]^{2\oplus}$$
(2) *(3)*

(1) can be oxidized to *(2)* and *(3)* in two reversible one-electron steps, $E_{1/2}=+0.36$ and $+0.97$ V (*versus* SCE, at Pt in 1 M $LiClO_4$/DMSO). The first reduction of *(1)* to *(4)* is also reversible. The potential difference of 1.84 V found between the first ring oxidation and ring reduction of TBP is much lower than that observed for other porphyrins, which usually exhibit differences of about 2.25 V[1]. The low first oxidation potential of *(1)* ($E_{1/2}=+0.36$ V) is remarkable; zinc octaethylporphyrin and zinc tetraphenylporphyrin are not oxidized below $E_{1/2}=+0.63$[3] and $+0.71$ V[4], respectively.

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Since porphyrin π radical ions warrant particular interest[5], we examined the species *(2)* more thoroughly[6]. Oxidation of *(1)* by iodine in methanol/dimethyl sulfoxide (10:1) affords *(2)* which has an absorption spectrum (Fig. 1) typical for porphyrin π radical cations[1, 5]. Species *(2)* can be completely reduced back to *(1)* (*e.g.* by dithionite).

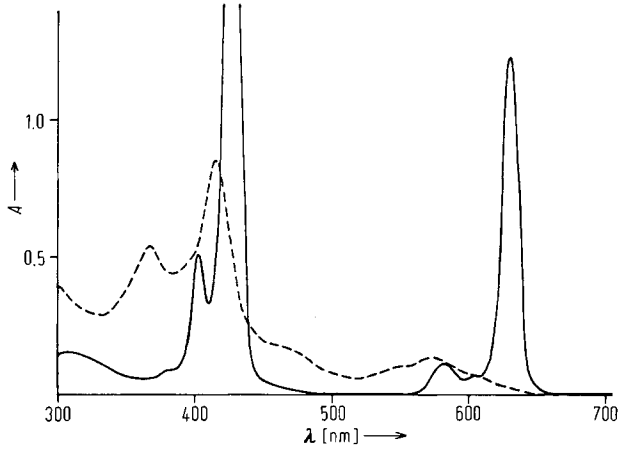


Fig. 1. Absorption spectrum of ZnTBP (——), 8.13×10^{-5} mol/l in methanol/dimethyl sulfoxide (10:1), 1-mm cuvette; after oxidation by iodine (----).

Further characterization of *(2)* was by ESR spectroscopy: in methanol/pyridine (10:1) the room temperature spectrum of *(2)* consists of a single line having a width of 5.5 G and a *g* value of 2.0029. No hyperfine structure could be observed at 77 K.

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Carbonyl(pyridine)iron(II) Tetrabenzporphyrin π-Radical Cation[**]

By *Arnd Vogler, Birgit Rethwisch, Horst Kunkely*, and *Jürgen Hüttermann*[*]

Iron porphyrins transfer electrons in biological systems. In cytochromes, electron transfer proceeds *via* the redox pair Fe^{II}/Fe^{III}. There are indications, however, that a π electron of the porphyrin ring participates in the initial step of such redox reactions[1]. While the oxidation of some Ru^{II} porphyrins does indeed lead to the loss of a porphyrin electron forming stable porphyrin π-radical cations[2], one-electron oxidation of Fe^{II} porphyrins has so far only been observed to give the corresponding Fe^{III} complexes[3]. This is because Fe^{II} is oxidized at lower potentials than the porphyrin ring, and Ru^{II} at higher potentials. If the oxidation potential of a porphyrin could be lowered below that of Fe^{II}, then it should be possible to obtain a stable Fe^{II} porphyrin π-radical cation. The existence of such a compound would be of interest not only in connection with the mechanism of biological reactions. A Fe^{II} porphyrin π-radical cation is isomeric ("oxidation state isomerism"[3]) with the corresponding Fe^{III} porphyrin; the two forms differ merely in the localization of an electron. In the case of the low spin Fe^{III} porphyrins known so far, the isomeric Fe^{II} porphyrin π-radical cation is a low energy, electronically excited CT state[4] to be observed in the absorption spectrum[5]. This CT state would become the new ground state in a stable Fe^{II} porphyrin π-radical cation.

We have now found that the oxidation of $[Fe^{II}(TBP)(CO)(py)]$ *(1)* (TBP = tetrabenzporphyrin) does indeed lead to the loss of a π electron from the porphyrin ligand to form $[Fe^{II}(TBP^{+})(CO)(py)]^{\oplus}$ *(2)*. The following criteria determine the choice of *(1)*: TBP has a very low oxidation potential[6] and the CO ligand stabilizes Fe^{II} relative to Fe^{III}[3]; thus the oxidation of Fe^{II} is shifted to higher potentials.

(1) was obtained by dissolution of $[Fe^{II}(TBP)(py)_2]$[7] in $CHCl_3$ saturated with CO. The IR spectrum of *(1)* in $CHCl_3$ shows a CO stretching band at 1975 cm^{-1}. Oxidation with iodine affords *(2)*, whose absorption spectrum (Fig. 1) is typical of porphyrin oxidation. The IR spectrum of *(2)* contains a νCO band at 2020 cm^{-1}. Fe^{III} carbonyl complexes are unknown. The 45 cm^{-1} shift occurring upon oxidation of *(1)* is probably due to the overall positive charge on *(2)*.

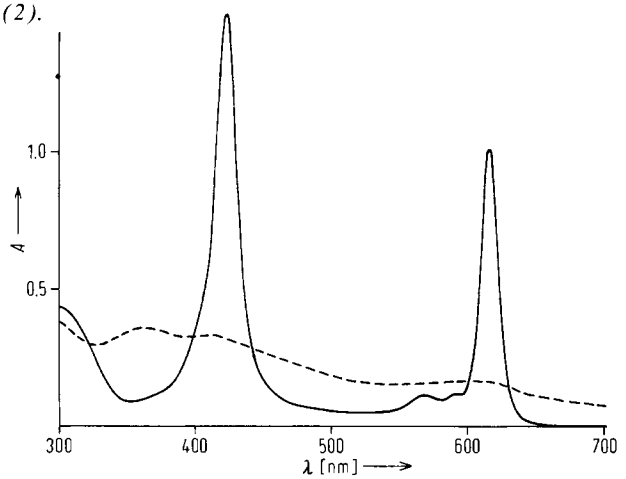


Fig. 1. Absorption spectrum of FeTBP(CO)(py) (——), 1.1×10^{-5} mol/l in $CHCl_3$, 1-cm cuvette; after oxidation by iodine (----).

The ESR spectrum of *(2)* in $CHCl_3$/methanol (1:1) consists of a single line having a width of 5.0 G and a *g* value of 2.0032. This signal, which only appears clearly below 77 K, closely resembles that of $[Zn(TBP^{+})]^{\oplus}$[6] and is completely different from the ESR spectra of the Fe^{III} porphyrins[8]. The reduction of *(2)* in dimethyl sulfoxide (*e.g.* by dithionite) completely regenerates *(1)*.

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(1), 68525-30-4; *(2)*, 68525-31-5; $Fe^{II}(TBP)(py)_2$, 22673-00-3

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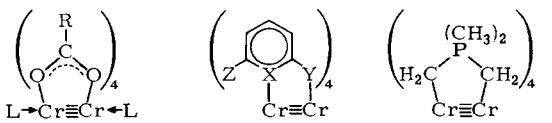
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A New Example of a Dichromium Compound with a Supershort CrCr Quadruple Bond[**]

By *F. Albert Cotton, Brian E. Hanson*, and *Gary W. Rice*[*]

The first compound now recognized to contain a quadruple bond, $Cr_2(O_2CCH_3)_4(H_2O)_2$, was discovered in 1844[1]. In 1970 it was shown[2] that the Cr—Cr distance is 2.3855(5) Å. More recently it has been shown[3] that Cr—Cr distances in 14 compounds of type *(1)* vary from 2.214(1) Å to 2.541(1) Å, this variability being consistent with the results of an SCF-HF-CI study[4]. However, it has also been known for several years that several quadruply bonded Cr_2^{4+} species have bond lengths slightly below 2.00 A, *viz.* $[Cr_2(CH_3)_8]^{4-}$ with 1.980(5) Å[5a], the closely similar $[Cr_2(C_4H_8)_4]^{4-}$ with 1.975(5) Å[5b] and $Cr_2(allyl)_4$ with *ca.* 1.97 Å[5c].



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

To complicate the picture further, it has been found in the last two years that species of type *(2)* (where the X, Y, Z atoms may be C, N, O, or S) have CrCr bond lengths in the range 1.830(4) Å to 1.889(1) Å; the shortest one of these is the shortest of all known metal-metal bonds[6]. Thus far, no explanation for the occurrence of such extremely short CrCr bonds in compounds of type *(2)* has been proposed, but the presence of an aromatic ring as the one common feature tended to suggest that the properties of that moiety might, in some way, be critical.

We wish to report here evidence that the presence of an aromatic ring is not essential to the occurrence of a "supershort" (< 1.90 Å) CrCr bond. The preparation of the compound $Cr_2[(CH_2)_2P(CH_3)_2]_4$ *(3)* was reported in 1974[7], but no structural information whatsoever has heretofore been available. We have now determined by X-ray crystallography[8] the molecular structure (Fig. 1). The familiar paddle wheel pattern of four bidentate bridging ligands forming five-membered rings with a common metal-metal axis is displayed; qualitatively, then, the structure is not surprising, although other possibilities existed[9]. The surprising and significant feature of *(3)* is the CrCr quadruple bond distance of 1.895(3) Å. This very short distance is found without the presence of any aromatic character in the ligand. The dimensions of the molecule are otherwise not unusual, the average values of the principal bond lengths and angles being Cr—C, 2.22(1) Å; P—C, 1.80(3) Å; Cr—Cr—C, 103.3(4)°; C—Cr—C, 87.0(6)°.

The fact that compound *(3)* contains a supershort CrCr bond is fortunate for several reasons. It is a molecular compound that is sufficiently volatile to allow measurements of its photoelectron spectrum either in the gas or solid phase, or both, as well as the ordinary electronic absorption spectrum. It is a simple enough molecule to permit detailed treatment of its electronic structure and bonding by both SCF-HF-CI and SCF-Xα-SW methods. In view of the difficulties encountered in obtaining and reconciling the results obtained by these two methods[4, 10] for the systems of type *(1)*, this will afford a welcome opportunity to enhance our comprehension of the theoretical aspects of metal-to-metal multiple bonds.

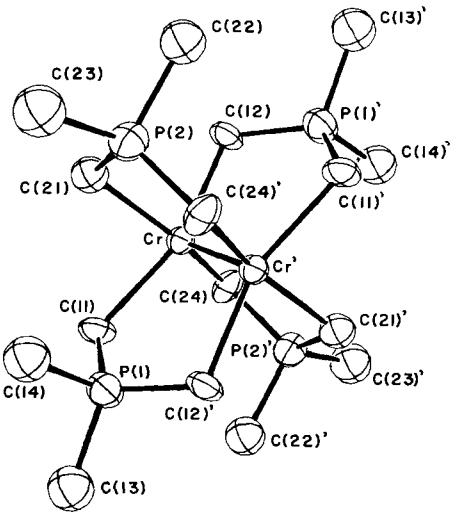


Fig. 1. The structure of the dichromium compound *(3)*; each atom is represented by its ellipsoid or sphere of thermal vibration, scaled to enclose 50% of its electron density [8].

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German version: Angew. Chem. *90*, 1015 (1978)
CAS Registry number:
(3), 68525-29-1

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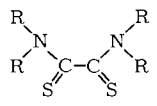
Thiooxalates as Dithiabutadienes

By *Klaus Hartke, Thomas Kissel, Josef Quante*, and *Günter Henssen*[*]

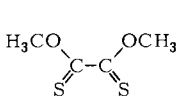
Thiocarbonyl compounds are known to react as 2π components in cycloadditions[1]. Examples of 1,2-dithiocarbonyl

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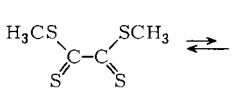
compounds as 4π components in cycloadditions have, to our knowledge, not been described[2]. We have now found that the dithionooxalate *(2)*[3] and the tetrathiooxalate *(3)*[4] undergo numerous cycloadditions owing to their very reactive dithiabutadiene system. These thioesters may function as 2π- or 4π-components, depending upon the reaction partner involved.



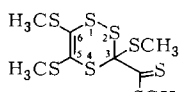
(1)



(2)



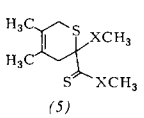
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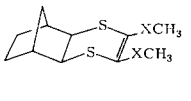
(4)

In the series *(1)*→*(3)*, the tetrathiooxalate *(3)* shows the least resonance stabilization and hence the highest reactivity. Thus, although *(3)* is monomeric in the crystalline form, in nonpolar solvents such as carbon tetrachloride and tetrahydrofuran the [4+2] dimer *(4)* is already present in equilibrium at room temperature up to about 20% [*(4)*, ^{1}H-NMR (CCl_4): δ=2.10 (C-3-SCH_3), 2.42 and 2.49 (C-5-, C-6-SCH_3), 2.68 (C(S)SCH_3); ^{13}C-NMR (CD_2Cl_2): δ=16.0, 17.8, 20.2, 21.6 (SCH_3), 88.4 (C-3), 132.8 and 133.6 (C-5, C-6), 231.2 (C=S)]. Other cycloaddition products with *(3)* are also formed under milder conditions than with *(2)*. As examples of [4+2] cycloadducts of *(2)* and *(3)*, the compounds *(5)*—*(13)* have been chosen; the experimental data are listed in Table 1.

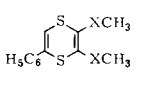
Table 1. Experimental data for the formation of cycloaddition products *(5)*—*(13)*. Owing to partial decomposition on distillation the liquid products (yellow oils) could only be purified by chromatography. All the compounds gave correct analyses and IR, ^{1}H-NMR, and ^{13}C-NMR spectra consistent with the quoted structures.



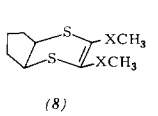
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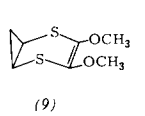
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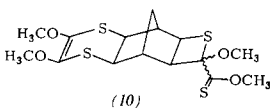
(7)



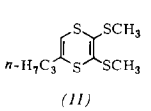
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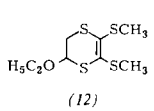
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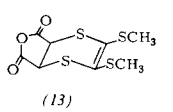
(10)



(11)



(12)



(13)

(a), X = O; *(b)*, X = S

Product	Starting compound	Reaction conditions	M.p. [°C]	Yield [%]
(5a)	*(2)* + 2,3-Dimethylbutadiene	in ether, reflux, 24 h	oil	100
(5b)	*(3)* + 2,3-Dimethylbutadiene	in CCl_4, 20°C, 3 h	56	100
(6a)	*(2)* + Norbornene	in ether, reflux, 6 h	33	77
(6b)	*(3)* + Norbornene	in CCl_4, 20°C, 1 h	56	80
(7a)	*(2)* + Phenylacetylene	without solvent, with $AlCl_3$	138	4
(7b)	*(3)* + Phenylacetylene	in CCl_4, reflux, 40 h	oil	*ca.* 80
(8a)	*(2)* + Cyclopentene	in cyclopentene, reflux, 3 d	oil	67
(8b)	*(3)* + Cyclopentene	in cyclopentene, 20°C, 72 h	oil	80
(9)	*(2)* + Cyclopropene	in CCl_4, 0°C, gaseous cyclopropene	52	75
(10)	*(2)* + Quadricyclane	in ether, 20°C, 35 h	132	87
(11)	*(3)* + 1-Pentyne	in 1-pentyne/CCl_4, reflux, 6 d	oil	*ca.* 50
(12)	*(3)* + Ethyl vinyl ether	in ethyl vinyl ether, 30 min	oil	90
(13)	*(3)* + Maleic anhydride	in CH_2Cl_2, 20°C, 2 d	102	90

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CAS Registry numbers:
(2), 54129-78-1; *(3)*, 61485-47-0; *(4)*, 68438-05-1; *(5a)*, 68438-06-2; *(5b)*, 68438-07-3; *(6a)*, 68438-08-4; *(6b)*, 68438-09-5; *(7a)*, 68438-10-8; *(7b)*, 68438-11-9; *(8a)*, 68438-12-0; *(8b)*, 68438-13-1; *(9)*, 68438-14-2; *(10)*, 68438-15-3; *(11)*, 68438-16-4; *(12)*, 68438-17-5; *(13)*, 68438-18-6; 2,3-dimethylbutadiene, 513-81-5; norbornene, 498-66-8; phenylacetylene, 536-74-3; cyclopentene, 142-29-0; cyclopropene, 2781-85-3; quadricyclane, 278-06-8; 1-pentyne, 627-19-0; ethyl vinyl ether, 109-92-2; maleic anhydride, 108-31-6

[1] a) *J. Sauer*, Angew. Chem. *78*, 233 (1966); Angew. Chem. Int. Ed. Engl. *5*, 211 (1966); b) *J. Hamer, J. A. Turner* in *J. Hamer:* 1,4-Cycloaddition Reactions. Academic Press, New York 1967, pp. 205ff.; c) *H. Wollweber*, Diels-Alder-Reaktion. Thieme, Stuttgart 1972; d) *E. Block:* Reactions of Organosulfur Compounds. Academic Press, New York 1978, pp. 278ff.
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[3] *K. Hartke, H. Hoppe*, Chem. Ber. *107*, 3121 (1974).
[4] *Th. Kissel, R. Matusch, K. Hartke*, Z. Chem. *16*, 318 (1976).

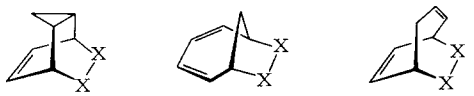
Norcaradiene and Cycloheptatriene Endoperoxides[**]

By *Waldemar Adam* and *Metin Balcı*[*]

Cycloheptatriene represents a fascinating and challenging substrate for cycloaddition. Thus its norcaradiene valence isomer could give [2+4] adducts of type *(A)*, whereas cycloheptatriene could yield the uncommon [2+6] adducts *(B)*, besides the more normal [2+4]-adducts *(C)*. We now report the successful preparation, isolation, and characterization of

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[**] Cyclic Peroxides, Part 77. Acknowledgments are made to the Donors of the Petroleum Research Fund (11022-AC-1) administered by the American Chemical Society, the National Science Foundation (CHE-78-12621), and the National Institutes of Health (GM-21119-03, GM-00141-04, and RR-8102-06).—Part 76: *W. Adam* and *K. Sakanishi*, Photochem. Photobiol., in press.



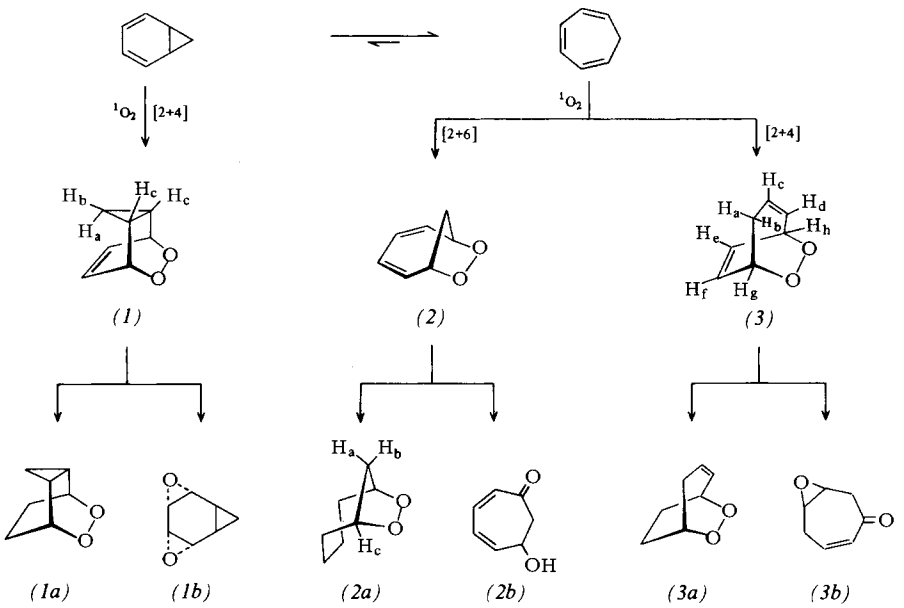
(A) (B) (C)

the endoperoxides *(1)*, *(2)*, and *(3)*—corresponding to types *(A)*, *(B)*, and *(C)*—produced by oxygenation of cycloheptatriene with singlet oxygen. To the best of our knowledge, this constitutes the first observation of all three possible Diels-Alder adducts in a cycloheptatriene cycloadditon.—Compound *(3)* has been isolated on photooxidation of cycloheptatriene in the presence of α-dicarbonyl compounds[1a]; *(2)* and *(3)* have been postulated as intermediates in the photooxygenation of cycloheptatriene with singlet oxygen[1b].

Photooxygenation of cycloheptatriene in CCl_4 (150-W Na lamp) at 0°C and tetraphenylporphyrin as sensitizer, followed by low temperature silica gel chromatography at −50 to −60°C (elution with CH_2Cl_2/pentane (1:1)) afforded *(1)*, *(2)*, and *(3)* in 3.5, 37, and 40% yield, respectively. The structure assignments of these unstable endoperoxides rests on ^{1}H-NMR and IR spectral data (Table 1). In addition, the following chemical transformations confirm the proposed structures.

The norcaradiene adduct *(1)* led to the saturated, bicyclic peroxide *(1a)* on diazene reduction in methanol at 0°C[2]. Furthermore, on heating in CCl_4 at 100°C in a sealed tube, *(1)* was converted into the hitherto unknown[3] isomer *(1b)* of norcaradiene diepoxide.

Treatment of the unusually strained [2+6] cycloadduct *(2)* with methanol at 30°C afforded the rearrangement product



(2b). For this reason the diazene reduction had to be carried out in the nonprotic solvent CH_2Cl_2 at *ca.* 0°C[4], resulting in the novel bicyclic peroxide *(2a)*.

Finally, diazene reduction at 0°C in methanol[2] of the [2+4] cycloadduct *(3)* led to the expected bicyclic peroxide *(3a)*. On heating in toluene at 180°C in a sealed tube *(3)* was converted into the epoxyenone *(3b)*.

The spectral and chemical data substantiate the novel endoperoxide structures beyond any reasonable doubt. Thus, *(1)* represents the first unsubstituted norcaradiene [2+4] cycloadduct, while *(2)* constitutes the first confirmed [2+6] cycloadduct with singlet oxygen. More significantly, photooxygenation of cycloheptatriene opens up a convenient entry to unusual bicyclic peroxides which are difficult to prepare by alternative routes.

Table 1. Selected physical data of compounds of types *(1)* to *(3)*. The ^{1}H-NMR and IR spectra were recorded in CCl_4 (except for *(2b)*, recorded in $CDCl_3$ and $CHCl_3$, respectively).

(1): Unstable, m.p. 64°C, yield 3.5%; ^{1}H-NMR: δ = 0.0—0.3 (m, 1H), 0.4—0.8 (m, 1H), 1.4—1.8 (m, 2H), 4.6—4.9 (m, 2H), 6.0—6.3 (dd, 2H); J_{AB} = 5.9 Hz, J_{BC} = 6.5 Hz, J_{AC} = 4 Hz; IR: 3070, 3040, 3000, 2900, 1530, 1440, 1370 cm^{-1}

(1a): M.p. 98°C, yield 85%; ^{1}H-NMR: δ = 0.45—1.0 (m, 2H), 1.05—2.2 (m, 6H), 4.0—4.4 (br. s, 2H); IR: 3030, 2945, 2860, 1465, 1350, 1300 cm^{-1}

(1b): n_D^{20} = 1.5062, yield 100%; ^{1}H-NMR: δ = 0.25—0.55 (m, 1H), 0.7—1.0 (m, 1H), 1.1—1.5 (m, 2H), 2.95 (s, 4H); IR: 2980, 1455, 1435, 1420, 1235 cm^{-1}; MS (70 eV): *m/e* = 124

(2): Unstable, n_D^{20} = 1.5316, yield 37%; ^{1}H-NMR: δ = 2.7—2.9 (q, 2H), 4.3—4.6 (m, 2H), 5.7—5.8 (m, 4H); IR: 3030, 2950, 1630, 1440, 1385, 1295 cm^{-1}

(2a): Semisolid, yield 72%; ^{1}H-NMR: δ = 0.9—2.0 (m, 8H), 2.1—2.8 (m, 2H), 4.2—4.6 (br. d, J_{BC} = 7.01 Hz, 2H); J_{AB} = 11.66 Hz, $J_{AC} \leq$ 1.3 Hz; IR: 2940, 1450, 1265, 1260 cm^{-1}

(2b) [1a]: Liquid, yield 90%; ^{1}H-NMR: δ = 2.4—3.5 (AB, 2H), 3.95 (s, 1H), 4.3—4.7 (m, 1H), 5.4—6.6 (m, 4H); IR: 3590, 3360, 3010, 1710, 1650, 1575 cm^{-1}

(3): Unstable, n_D^{20} = 1.5249, yield 40%; ^{1}H-NMR: δ = 2.0—3.1 (AB, 2H), 4.2—4.7 (m, 2H), 5.2—6.7 (m, 4H); J_{AB} = 18.6 Hz, $J_{AC} \approx J_{BC}$ = 3 Hz, J_{AG} = 2.3 Hz, J_{BG} = 3.99 Hz, J_{CD} = 10.6 Hz, J_{EF} = 9.3 Hz; IR: 3070, 3040, 2940, 2890, 1650, 1415 cm^{-1}

(3a): M.p. 32—33°C, yield 30%; ^{1}H-NMR: δ = 1.2—2.4 (m, 4H), 2.2—3.1 (AB, J_{AB} = 16.6 Hz, 2H), 4.1—4.5 (m, 2H), 5.5—5.9 (m, 2H); IR: 3045, 2970, 1650, 1460, 1420, 1345 cm^{-1}

(3b): n_D^{20} = 1.5269, yield 82%; ^{1}H-NMR: δ = 2.2—3.5 (m, 6H), 5.5—6.5 (m, 2H); IR: 3030, 3010, 2960, 1690, 1580, 1440 cm^{-1}

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[2] *W. Adam, H. J. Eggelte*, Angew. Chem. *89*, 762 (1977); Angew. Chem. Int. Ed. Engl. *16*, 713 (1977).
[3] *E. Vogel, H. J. Altenbach, E. Schmidbauer*, Angew. Chem. *85*, 862 (1973); Angew. Chem. Int. Ed. Engl. *12*, 838 (1973).
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syn,syn-1,6:8,17:10,15-Trismethano[18]annulene

By *Wolfgang Wagemann, Masahiko Iyoda, Hans M. Deger, Johannes Sombroek*, and *Emanuel Vogel*[*]

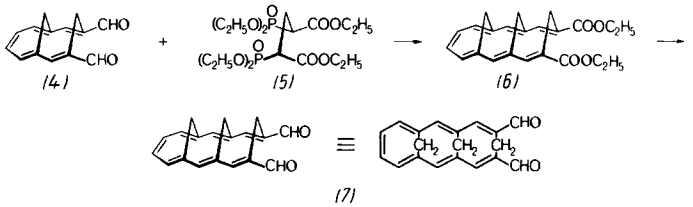
Dedicated to Professor Heinrich Hellmann on the occasion of his 65th birthday

Interestingly, *syn*-1,6:8,13-bismethano[14]annulene *(2)*[1], the next higher homologue (*syn*-series) of 1,6-methano-[10]annulene *(1)*, has been shown to be a Hückel aromatic, although steric interaction of the inner bridge hydrogen atoms in *(2)* causes appreciable bending of the annulene ring[2]. This finding is of interest from both the theoretical as well as the synthetic standpoint and called for extension of the [4*n*+2]annulene series *(1)*, *(2)*, *(3)*, *etc.* beyond *(2)*, in particular to establish more accurately, the position of the bridged [4*n*+2]annulenes with an acene perimeter between the acenes on the one hand and the [4*n*+2]annulenes of *Sondheimer*[3a], *Nakagawa*[3b], and *Boekelheide*[3c] on the other.



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

For synthesis of the 18π homologue of *(1)* and *(2)*, *i.e.* *syn,syn*-1,6:8,17:10,15-trismethano[18]annulene *(3)*, which we report here, the conformational features of the known bicyclo[5.4.1]dodeca-2,5,7,9,11-pentaene-3,5-dicarbaldehyde[1] have served as a guide. Since this α,ω-pentaenedialdehyde exists as the *syn*-conformer *(4)*, the homologous α,ω-heptaenedialdehyde ought also to exist in the *syn*-conformation [*(7)*] and thus represent an ideal synthon for *(3)*.

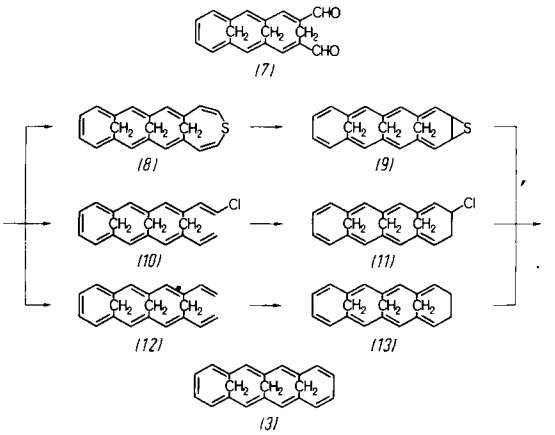


(4) *(5)* *(6)* *(7)*

To synthesize the carbon skeleton of the heptaenedialdehyde, *(4)* was allowed to react with the Horner-Wittig reagent 1,3-diethoxycarbonyl-1,3-propanylenebis(diethylphosphonate) *(5)*, readily obtainable by Michaelis-Arbuzov reaction of diethyl α,α'-dibromoglutarate with triethyl phosphite[4] (generation of the biphosphonate dicarbanion with sodium hydride in ether; olefination conditions: dichloromethane/benzene, reflux, 3 h). Although ring closures with difunctional olefinating agents usually proceed unsatisfactorily we obtained the heptaene diester *(6)* in 58% yield [orange-red needles (methanol), m. p. 162—163 °C] after chromatography on silica gel. Reduction of the diester with diisobutylaluminum hydride (benzene, room temperature) led to the corresponding diol [yellow needles (acetone), m. p. 211—212 °C (decomp.), yield 71%], which on oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (= DDQ; dioxane, room temperature) gave the dialdehyde *(7)* [red needles (dichloromethane), m. p. 264—267 °C (decomp), yield 75%]. That the dialdehyde was present as the expected *syn*-conformer, both in the crystalline state and in solution, was confirmed by X-ray structure analysis[5] and by the chemical transformations of the compound.

Our concept for the subsequent synthetic route to *(3)* was as follows[4]: olefination of *(7)* to give an appropriately terminally substituted nonaene and "cyclodehydrogenation" of this product by a sequence of disrotatory 18π electrocyclic process[6] and β-elimination.

On the basis of previous successful experiments[1], an attempt was made to react *(7)* with the difunctional Wittig reagent formed from thiodimethylenebis(triphenylphosphonium bromide) and lithium methoxide to give the thia[19]annulene *(8)*, since *(8)* was expected to be readily convertible into *(3)* *via* the [18]annulene episulfide *(9)*. Despite variation of the reaction conditions we have so far been able to obtain *(3)* only in traces (<1%) *via* this route.



(7) *(8)* *(9)* *(10)* *(11)* *(12)* *(13)* *(3)*

As an alternative approach we considered the consecutive olefination of *(7)* by two judiciously selected monofunctional Wittig reagents: the monovinyl compound [carmine-red platelets (ethyl acetate), decomp. 178—180 °C; IR: 1665 cm^{-1} (C=O); yield 55%] initially obtainable as main product of reaction with methylene(triphenyl)phosphorane (molar ratio 1:1.2) in tetrahydrofuran (room temperature, 3 h), can be converted by reaction with chloromethylene(triphenyl)phosphorane[7] in tetrahydrofuran (−70 °C, then room temperature, 3 h) into *(10)* [mixture of *cis/trans* isomers, yellow crystals (ethyl acetate/chloroform); m/e = 306 (^{35}Cl) (M^+, base peak); yield 70%]. In boiling dimethylformamide (90 min), *(10)* smoothly cyclizes to *(11)*, which spontaneously undergoes dehydrohalogenation with formation of *(3)*[8] [yield 83% of NMR spectroscopically pure, crystalline hydrocarbon after chromatographic filtration on aluminum oxide Act. III (hexane/dichloromethane 8:1)]. Regarding the combination of the 18π electrocyclic process with a dehydrogenation step it would appear that the divinyl compound *(12)* [yellow crystals (ethyl acetate/chloroform), decomp. >180 °C; yield 75%] obtainable from *(7)* and methylene(triphenyl)phosphorane (molar ratio 1:3) could serve as a useful nonaene intermediate. Indeed, *(12)* afforded the annulene when it was thermolyzed (yield 40%; after chromatography) with DDQ (molar ratio 1:1.4) in anisole (quartz ampoule; 270 °C, 7 min). Attempts to detect *(13)*, the dihydro[18]annulene precursor of *(3)*, have so far failed. The new [18]annulene *(3)* crystallizes from toluene[9] as golden-brown scales (decomp. >180 °C); in contrast to *(1)* and *(2)* it is air-sensitive and is storable only at low temperature (under protecting gas). The olefinic reactivity of *(3)* is determined more by Baeyer- and Pitzer-strain than by loss of resonance, for according to its spectroscopic properties the hydrocarbon exhibits distinct aromatic character.

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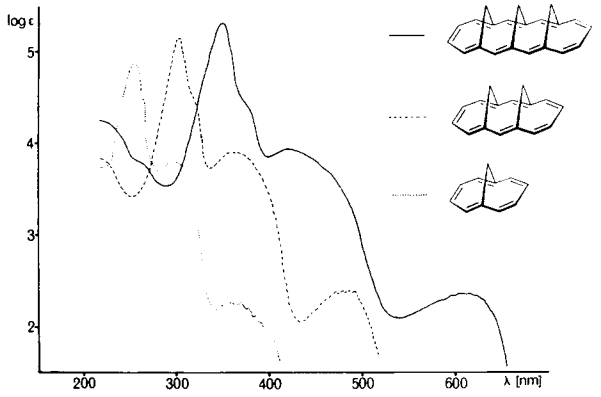
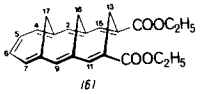


Fig. 1. Electronic spectra of *(1)*, *(2)*, and *(3)* in cyclohexane.

That *(3)* is to be regarded as aromatic is supported quite impressively by the relationship of its electronic spectrum to those of its lower homologues *(1)* and *(2)* (Fig. 1). The spectra of the three annulenes are remarkably similar in shape but on progression from [10]- to [14]- to /18]annulene all of the bands undergo bathochromic shifts, as theoretically predicted. The NMR spectrum of *(3)* (Table 1), showing a downfield position of the resonances of the annulene protons and an upfield position of the resonances of the bridge protons, is indicative of a diamagnetic ring current and, moreover, due to its absorption pattern, affords evidence that the expected *syn-syn*-stereoisomer having C_{2v} symmetry is present, and not the *syn,anti*-isomer, likewise compatible with the configuration of *(7)*. This stereochemical result follows independently from the marked positive nuclear Overhauser effect[10] which the doublet of the inner protons of the two terminal CH_2 bridges experiences when irradiated with the resonance frequency of the protons of the central CH_2 bridge.

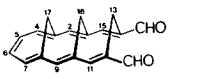
It follows from a comparison of the chemical shifts of the corresponding bridge protons in *(3)* and *(2)* that the steric compression of the inner bridge protons and consequently the relevant H—H distances [1.78 Å in the case of *(2)*[2]] are very similar in the two annulenes. Considering the rigidity of the carbon skeleton in annulenes of this type, which hardly permits any notable deviation of the molecule from the C_{2v} symmetry, this finding enables the molecular architecture of *(3)*, especially the curvature (or bending) of its annulene ring to be derived with a great degree of certainty[11].

Table 1. Spectral data of the diester *(6)*, the dialdehyde *(7)*, the divinyl compound *(12)*, and the *syn,syn*-1,6:8,17:10,15-trismethano[18]annulene *(3)*.



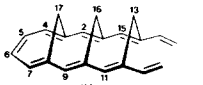
(6)

UV (dioxane): λ_{max} = 317 nm (ε = 81 200), 339 (sh, 68 900), 397 (5650); IR (CsI): 1695 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ = −0.36 and 3.17 (AX system, J = 12.9 Hz, 2H, H-17), 3.35 and 4.22 (AX system, J = 15.9 Hz, 2H, H-16), 3.94 and 4.97 (AX system, J = 16.5 Hz, 2H, H-13), 6.92 (s, 2H, H-2, 9), 7.20—6.78 (AA'XX' system, 4H, H-4, 5, 6, 7), 7.45 (s, 2H, H-11, 15), 1.29 and 4.22 (t and q, 10H, $2C_2H_5$).



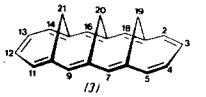
(7)

UV (dioxane): λ_{max} = 326 nm (ε = 80 900), 334 (81 600), 409 (5300); IR (CsI): 1668 cm^{-1} (C=O); ^{1}H-NMR ($C_2D_2Cl_4$): δ = −0.22 and 3.27 (AX system, J = 13.2 Hz, 2H, H-17), 3.43 and 4.37 (AX system, J = 15.3 Hz, 2H, H-16), 3.53 and 4.85 (AX system, J = 16.2 Hz, 2H, H-13), 6.75—7.22 (AA'XX' system and 2s, 8H, H-2, 4, 5, 6, 7, 9, 11, 15), 9.22 (s, 2H, 2CHO).



(12)

UV (dioxane): λ_{max} = 228 nm (ε = 14 100), 323 (113 000), 337 (sh, 76 600), 406 (5700); IR (CsI): 1606, 1529 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$): δ = −0.42 and 3.15 (AX system, J = 13.5 Hz, 2H, H-17), 3.37 and 4.30 (AX system, J = 15.6 Hz, 2H, H-16), 3.79 and 4.17 (AX system, J = 16.2 Hz, 2H, H-13), 5.03 (d, 2H), 5.54 (d, 2H) and 6.39 (m, 2H) (ABX system of the protons of the vinyl groups), 6.32 (s, 2H, H-11, 15), 6.77 (s, 2H, H-2, 9), 6.83—7.17 (AA'XX' system, 4H, H-4, 5, 6, 7).



(3)

UV (cyclohexane): λ_{max} = 258 nm (sh, ε = 6300), 349 (195 000), 373 (sh, 26 500), 422 (8400), 589 (sh, 200), 596 (sh, 218), 605 (229), 614 (sh, 221), 625 (sh, 203), 637 (sh, 151); IR (CsI): 1540 cm^{-1} (C=C); ^{1}H-NMR (CD_2Cl_2): δ = −0.45 and 1.32 (AX system, J = 13.5 Hz, 4H, H-19$_{exo}$, H-21$_{exo}$ *e.g.* H-19$_{endo}$, H-21$_{endo}$), 0.53 (s, 2H, H-20), 6.70—7.70 (AA'XX' system, 8H, H-2, 3, 4, 5, 11, 12, 13, 14), 7.62 (s, 4H, H-7, 9, 16, 18).

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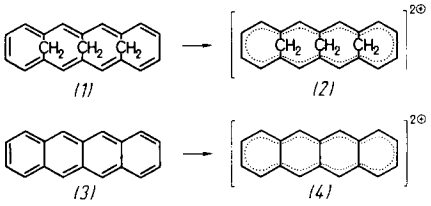
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[5] *T. Pilati, M. Simonetta*, Acta Crystallogr. *B33*, 851 (1977).
[6] *R. B. Woodward, R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. Int. Ed. Engl. *8*, 781 (1969); *R. Huisgen*, Chim. Ind. (Milan) *51*, 963 (1969).—The cyclizations of *(8)*, *(10)*, and *(12)* to the corresponding dihydro[18]annulenes, interpreted here as disrotatory 18π-electrocyclic processes, can be alternatively explained in terms of a 6π-electrocyclic process (cycloheptatriene-norcaradiene isomerization) followed by a number of Cope rearrangements equal to the number of bridges.
[7] *G. Köbrich, H. Trapp, K. Flory, W. Drischel*, Chem. Ber. *99*, 689 (1966).
[8] It could be shown by thermolysis of the β,β-dideuteriovinylchlorovinyl compound that the cyclization of *(10)* does not proceed *via* an acetylene intermediate. This finding warrants mention, since in the meantime it has been found that the ethynylvinyl compound also gives *(3)* on thermolysis (unpublished experiments in collaboration with *M. Hanelt*); cf. also the benzene synthesis by thermal cyclization of 1,3-hexadien-5-yne described by *H. Hopf* and *H. Musso*, Angew. Chem. *81*, 704 (1969); Angew. Chem. Int. Ed. Engl. *8*, 680 (1969).
[9] Other solvents have proved less suitable; on recrystallization of the NMR-spectroscopically pure annulene *(3)* from toluene (−20 °C) *ca.* 50 % of the substance remains in the mother liquor.
[10] *G. E. Bachers, T. Schaefer*, Chem. Rev. *71*, 617 (1971).
[11] An X-ray structure analysis of compound *(3)* has so far been impossible due to the state of the crystals (thin, flaky platelets).

syn,syn-1,6:8,17:10,15-Trismethano[18]annulene Dication— Dication of a [4*n*+2]Annulene

By *Hans M. Deger, Klaus Müllen*, and *Emanuel Vogel*[*]

The dications of polycyclic arenes, which can be regarded as 4*n*π electron systems, have been known for some time[1,2]. Annulene dications have also been described on a number of occasions[3]; however, in this case, all the species studied—with exception of the hexachlorobenzene dication[4]—have been aromatic (4*n*+2)π-electron systems derived from [4*n*]annulenes. The formal structural relationship between *syn,syn*-1,6:8,17:10,15-trismethano[18]annulene *(1)*[5] and naphthacene *(3)*, which is oxidized to *(4)* in superacid solution[2a], would suggest [4*n*+2]annulene *(1)* as being a possible candidate for the formation of a potentially antiaromatic dication.

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(1) (2)

(3) (4)

Addition of *(1)* in dichloromethane to a solution of fluorosulfonic acid in SO_2ClF cooled to $-80°C$ leads to a violet reaction mixture whose color changes irreversibly to olive-green on warming to 0°C. The NMR spectra of this solution, which can be stored for weeks in a sealed tube at $-20°C$, show that the dication *(2)* is indeed present[6, 7].

The main supporting evidence for the existence of *(2)* is afforded by the seven-line ^{13}C-NMR spectrum (Fig. 1), from which it follows that the C_{2v} symmetry of the starting material is retained in the product. The downfield shift of the center of the ring carbon signals observed during conversion of *(1)* into *(2)* is 17.7 ppm and thus corresponds to the value expected owing to the deshielding effect of the two positive charges in *(2)*. Since the shifts of the signals of the C atoms 7, 9, 16, and 18 are most pronounced, it may be assumed—by analogy with the situation in the naphthacene dication *(4)* and in agreement with MO calculations—that a build up of charge occurs at these positions.

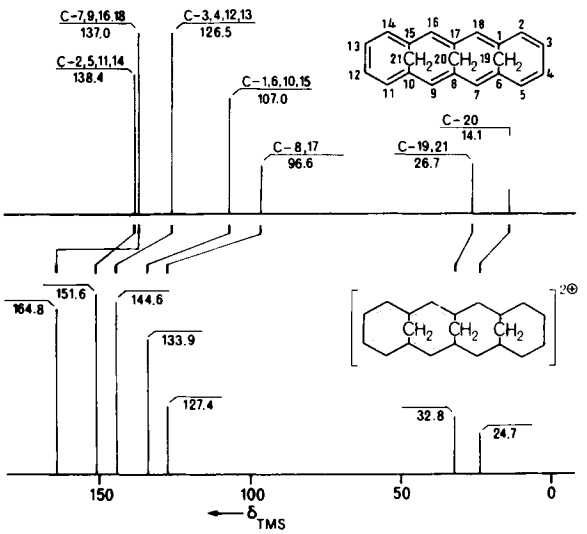
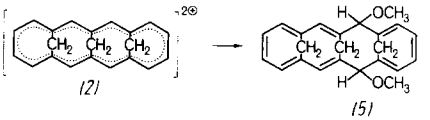


Fig. 1. Schematic representation of the ^{13}C-NMR spectra of *(1)* and *(2)*.

In agreement with the expectation that the dication *(2)* (as a $4n\pi$-electron system) exhibits a paramagnetic ring current, the resonances of the bridge protons in the ^1H-NMR spectrum of *(2)* [$(SO_2ClF/CD_2Cl_2/FSO_3H, -10°C)$: $\delta = 4.35$ and 7.58 (AX system, $J = 14.4$ Hz, 4H, H-19, 21), 6.07 (s, 4H, H-7, 9, 16, 18), 7.01—7.35 (AA'XX'' system, 8H, H-2, 3, 4, 5, 11, 12, 13, 14), 8.25 (s, 2H, H-20)] appear considerably further downfield than those of *(1)*. In contrast there is essentially no difference between the spectra of *(2)* and *(1)* as regards the resonance positions of the annulene protons. This is understandable if one assumes that an upfield shift of the annulene protons due to the ring current in *(2)* is compensated by the influence of the positive charge.



(2) (5)

Chemical evidence for the existence of *(2)* was provided by the isolation of a solvolysis product: on treatment of a solution of *(2)* in dichloromethane at $-80°C$ with methanol and subsequent chromatography of the mixture on silica gel (dichloromethane/ether/hexane, 1:1:2) a dihydrodimethoxy derivative of *(1)* is obtained [bright yellow rhombohedra, m. p. 205—206°C (methanol/ethyl acetate); yield 13%], which according to the spectra has the structure *(5)* with *cis* arrangement of the methoxy groups[8] [^1H-NMR ($CDCl_3$): $\delta = 0.00$ and 3.75 (AX system, $J = 12$ Hz, 2H, H-19), 1.09 and 4.25 (AX system, $J = 15$ Hz, 2H, H-21), 3.75 and 4.22 (AX system, $J = 12$ Hz, 2H, H-20), 3.98 (s, 2H, H-7, 18), 5.70—5.84 and 6.18—6.37 (AA'XX' system, 4H, H-2, 3, 4, 5), 6.05 (s, 2H, H-9, 16), 6.18—6.37 and 6.67—6.82 (AA'XX' system, 4H, H-11, 12, 13, 14), 3.37 (s, 6H, $2OCH_3$)].

It is conceivable that the oxidation of $[4n+2]$annulenes to dications is not restricted to the example described here, but is a general reaction for higher $[4n+2]$annulenes.

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[6] The mechanism of the oxidation of *(1)* to *(2)* is still an open question. We are currently carrying out investigations in an attempt to elucidate whether a σ-complex is initially formed or whether the reaction proceeds *via* a radical cation. The reaction of *(1)* with antimony pentafluoride in SO_2ClF, which also leads to *(2)*, might involve a radical cation mechanism.

[7] As already found by *P. Warner* and *S. Winstein*, under the conditions employed for the generation of *(2)* from *(1)*, 1,6-methano[10]annulene affords a stable σ-complex, cf. J. Am. Chem. Soc. *91*, 7785 (1969).

[8] From the spectra it is not certain which configuration the methoxy groups assume with respect to the CH_2 bridges. An X-ray structure analysis is expected to resolve this problem.

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